

Air pollution and stroke in a bi-ethnic community: Associations with incidence, recurrence and stroke severity

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in The University of Michigan
2015

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Acknowledgements

First and foremost, I want to thank my advisor Dr. Lynda Lisabeth for all of her support, motivation and inspiration every step of the way. I know that I would not have made it this far without her. I want to thank her for accepting me into the program and challenging me to step out of my comfort zone.

I also want to thank Dr. Sara Adar for her thoughtful feedback and for the brainstorming efforts in her office when our results just did not make sense. Thank you, Dr. Lewis Morgenstern, for sitting down with me and making me read “The Big Stroke Book”. His patience through that process and support pushed me to keep going. And for my last committee member, Dr. Brisa Sanchez, if not for her, I would not have pursued a doctorate. I was very fortunate the day Dr. Trivellore Raghunathan told me that I would be working with her, because she introduced me to stroke research and always kindly nudged me toward a Ph.D. (even though I think she was suggesting one in a different department).

I want to acknowledge my funding sources, for without them, returning to school would have been financially impossible. Thank you, Brisa and KT for allowing me to work on your projects. Thank you to the Epidemiology Department and Rackham for making travel to conferences feasible. And the American Heart Association Predoctoral Fellowship who covered my last year in the program. And thank you to my wife, who covered my allowance and allowed me to do fun things.

I was lucky enough to have a great support system along the way. Thank you Epidocs-2011, for integrating me into the program and thank you to the CSEPH family for always being

supportive and there for a needed distraction. A special thank you to Amanda Dudley, whose knowledge of any- and everything makes every hoop that much easier to jump through. Thank you to my academic siblings, Sarah and Dayna, for being sounding boards and to help interpret comments from our mom. Thank you, Paul, Helen and Paulina, for always being amenable to lunch beers on both good and bad days.

Thank you to my friends and family, who while they might not understand what I do, they have supported me every step of the way and built me back up when I needed a push. Thank you to my Dad, who placed so much value on education, that I dedicate this work to him. And last, but certainly not least, thank you to my wife and biggest supporter, Mary Kate. Thank you for letting me always make you dinner, no matter how busy I was with school.

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List of Abbreviations

AF	Atrial fibrillation
BASIC	Brain Attack Surveillance in Corpus Christi
CAD	Coronary artery disease
EPA	Environmental Protection Agency
MA	Mexican American
NAAQS	National Ambient Air Quality Standards
NHW	Non-Hispanic white
NIHSS	National Institutes of Health Stroke Scale
NOAA	National Oceanic and Atmospheric Administration
O ₃	Ozone
PM _{2.5}	Particulate matter less than 2.5 µm in aerodynamic diameter
SES	Socioeconomic status
TAMIS	Texas Air Monitoring Information System
TCEQ	Texas Commission on Environmental Quality
TEOM	Tapered element oscillating microbalance
TIA	Transient ischemic attack

Abstract

Stroke is a leading cause of disability in the United States and costs related to stroke are enormous. Much is known about individual level risk factors for stroke and stroke severity, but less is known about environmental risk factors. Air pollution may be an aspect of the environment that contributes to stroke risk, but current evidence is inconsistent. The overarching aim of this dissertation was to advance the current understanding of the associations between features of the environment and ischemic stroke (both incident and recurrent) and stroke severity. Specifically, this dissertation investigated 1) ambient air pollution (particulate matter < 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) and ozone (O_3)) and incident stroke and the potential effect modification by Mexican American (MA) ethnicity, 2) ambient air pollution and recurrent stroke and the identification of susceptible sociodemographic or clinical subgroups, and 3) both ambient air pollution and neighborhood disadvantage and their potential synergistic effects on initial stroke severity.

Stroke cases were obtained from the population-based Brain Attack Surveillance in Corpus Christi (BASIC) project from 2000-2012, air pollution data was identified from the Texas Commission on Environmental Quality's Texas Air Monitoring Information System, and neighborhood disadvantage was created from census data. A time-stratified case-crossover design and conditional logistic regression methods were used to investigate associations between air pollutants ($\text{PM}_{2.5}$ and O_3) and both incident and recurrent strokes. Associations between air

pollution and neighborhood disadvantage and stroke severity were examined using traditional regression methods accounting for individual clustering within neighborhoods.

Weak associations between higher short-term O₃ exposures and increased odds of incident ischemic stroke were demonstrated, but no significant associations were observed between previous-day levels of PM_{2.5} and O₃ and recurrent ischemic stroke. Stronger associations between O₃ and incident stroke were observed only among non-Hispanic whites (NHWs). Although some modifications were suggested, effect modification of the air pollution-recurrent stroke association by sociodemographic and clinical factors was not observed consistently across the two pollutants. Findings suggested that living in an area of high neighborhood disadvantage increases the likelihood of a severe ischemic stroke compared to living in an area of low neighborhood disadvantage, and an association between PM_{2.5} and severe stroke was only evident in areas of high neighborhood disadvantage. Higher O₃ levels were associated with severity; however, this association did not vary by neighborhood disadvantage.

The culmination of this dissertation suggests that environmental factors influence stroke risk and severity. Future studies are necessary to understand the association between air pollution and stroke, how the association may vary by ethnicity, differential susceptibility to air pollutants, and to promote environmental justice for disadvantaged neighborhoods that may not have the ability to protect themselves.

Chapter 1

Introduction

1.1 Introduction

Stroke is the fourth leading cause of death and leading cause of adult disability in the United States (US), costing almost \$54 billion annually.^{1,2} Initial stroke severity is an important predictor of stroke outcomes, including functional outcomes³⁻⁶ and mortality.⁷ Individual risk factors for stroke and stroke severity have been identified,^{8,9} but less is known about environmental risk factors. Inconsistent evidence exists regarding the influence of air pollution on stroke risk,¹⁰⁻¹⁴ and this work has been conducted in predominantly non-Hispanic white populations and cannot inform questions of enhanced susceptibility by race/ethnicity. Further, the influence of air pollution on stroke severity is unclear, with only two studies to date examining this association.^{15,16} Neighborhood disadvantage may also influence stroke severity,¹⁷ and could influence susceptibility to air pollution, via lack of healthy foods,¹⁸ reduced access to medications,¹⁹ or co-exposure to other pollutants.^{20,21} Identification and understanding of the multiple levels of influence on stroke risk and severity could suggest new avenues to reduce stroke burden.

The objective of this dissertation was to advance the understanding of the associations between features of the environment and ischemic stroke. Specifically, we investigated associations between ambient air pollution (particulate matter < 2.5 μm in aerodynamic diameter (PM_{2.5}) and ozone (O₃)) and both incident and recurrent stroke. The air pollution-stroke associations were further investigated for differential susceptibility by ethnicity (incident stroke)

and sociodemographic and clinical factors (recurrent stroke). The influences of air pollution and neighborhood disadvantage on initial stroke severity were additionally explored. The research used stroke data from the Brain Attack Surveillance in Corpus Christi (BASIC) Project, a population-based stroke surveillance study in Nueces County, Texas from 2000 to 2012 in combination with air pollution and meteorological data from the Texas Commission on Environmental Quality's (TCEQ) Texas Air Monitoring Information System (TAMIS)²² and from the National Oceanic and Atmospheric Administration (NOAA)²³ and Census data.

1.2 Specific Aims and Hypotheses

Specific Aim 1: To investigate the associations between air pollutants ($PM_{2.5}$ and O_3) and risk of incident ischemic stroke and to determine if the associations are modified by ethnicity using a case-crossover design in the BASIC Project.

Hypothesis 1a: Higher levels of $PM_{2.5}$ and O_3 will be associated with greater risk of incident ischemic stroke.

Hypothesis 1b: Ethnicity modifies the associations between $PM_{2.5}$ and O_3 and incident ischemic stroke, such that the associations are greater in Mexican Americans compared with non-Hispanic whites.

Specific Aim 2: To determine the associations between air pollutants ($PM_{2.5}$ and O_3) and the risk of recurrent ischemic stroke and to identify whether these associations are modified by sociodemographic and clinical factors using a case-crossover design in the BASIC Project.

Hypothesis 2a: Higher levels of $PM_{2.5}$ and O_3 will be associated with greater risk of stroke recurrence.

Hypothesis 2b: The associations between PM_{2.5} and O₃ and stroke recurrence are modified by sociodemographic and clinical factors, such that there are subgroups that are more susceptible to the influence of PM_{2.5} and O₃ on stroke recurrence.

Specific Aim 3: To investigate the associations between neighborhood disadvantage and air pollutants (PM_{2.5} and O₃) and initial stroke severity and whether neighborhood disadvantage modifies the association between air pollution and severity in the BASIC Project.

Hypothesis 3a: Higher levels of neighborhood disadvantage, PM_{2.5} and O₃ will be associated with greater initial stroke severity.

Hypothesis 3b: Neighborhood disadvantage modifies the association between PM_{2.5} and O₃ and initial stroke severity, such that the association is greater in more disadvantaged neighborhoods compared to less disadvantaged neighborhoods.

1.3 Background

Public Health Importance of Stroke

An estimated 795,000 people have a stroke each year, with approximately 610,000 being incident events.¹ Stroke is a leading cause of disability and is estimated to cost almost \$54 billion annually, in the US,^{1,2} with severe strokes costing as much as two times that of mild strokes in acute hospital settings.²⁴ Ischemic strokes are the most common type of stroke in the US, accounting for 87% of all strokes with intracerebral hemorrhages accounting for 10% and subarachnoid hemorrhages accounting for 3%.¹ On average, a stroke death occurs every four minutes, making it the fourth leading cause of death in the US.¹

Almost a quarter of all strokes are recurrent events,²⁵ with estimates of the 1-year cumulative risk of recurrence range from 7 to 13%.^{9,26–31} Recurrent strokes are associated with worse outcomes and greater mortality relative to first strokes.^{32–35} Over the last century, stroke

mortality has declined considerably resulting in an increasing population of stroke survivors who are at risk for multiple stroke events.³⁶ Projections suggest that by 2030 the number of stroke survivors will increase by 3.4 million from 2012, signifying stroke recurrence will take on increasing public health importance.³⁷

Pathophysiology of Ischemic Stroke

Ischemic stroke and cerebral ischemia occur as a result of decreased or disrupted blood flow to the brain. This reduced blood flow is most commonly a result of atherosclerosis causing local damage to a vessel wall. Atherosclerosis is a chronic lifetime process of the buildup of plaque in the arteries, narrowing and reducing blood flow.³⁸ Atherosclerotic development begins with endothelial injury and inflammation, which can be induced by oxidative stress, causing the oxidation of low-density lipoproteins (LDL) and promoting injury. Oxidized LDL is toxic to endothelial cells and penetrates into the intima of the arterial wall.³⁹ Monocytes adhere to the endothelial cells and T-lymphocytes become activated, leading to transformation into a foam cell (macrophages filled with oxidized LDL). When the foam cells accumulate, they form a fatty streak, which produces more toxic oxygen radicals, compounding the inflammation and progressive damage to the arterial wall.⁴⁰ Over time, the plaque becomes fibrous and thick and begins to occlude the lumen of the vessel. Blood platelets can adhere to the plaque, and release pro-thrombotic factors forming a clot or thrombus. The thrombus can break off and travel to a distal vessel or remain and occlude the vessel. Emboli that result from cardiac origin, either due to atrial fibrillation or recent myocardial infarction, are referred to as cardioembolic strokes.^{41–43}

Ethnic Disparities in Stroke

The burden of stroke is not equally distributed among the population. Mexican Americans (MA) have a 24% greater stroke risk compared to non-Hispanic whites (NHW;

relative risk (RR):1.24; 95% confidence interval (CI):1.12-1.37) in individuals older than 45 years of age.⁴⁴ This difference is more pronounced in younger ages, with MAs between 45-59 having more than double the risk of same aged NHWs (RR: 2.10; 95% CI: 1.64-2.69).⁴⁴ Recurrence rates have also been found to differ by ethnicity, with MA having a 57% increased risk of stroke recurrence relative to NHWs (95% CI: 1.05-2.34).⁴⁵

MAs differ from NHWs with respect to their stroke risk factor profiles. MAs have almost a threefold increased risk of diabetes⁴⁶ (odds ratio (OR): 2.7; 95% CI: 2.0-3.7) compared with NHWs.⁴⁷ MAs also have greater socioeconomic disadvantage with more than a six-fold increase in the odds of earning an income less than \$20,000 per year, and are less likely to have graduated from high school when compared to NHWs.⁴⁷ Even though MAs have these inflated risks with respect to stroke, MAs are less likely to have atrial fibrillation compared to NHWs and hypertension prevalence is similar between the ethnic groups.⁴⁷ Therefore, these traditional risk factors likely account for some but not all of the stroke disparity between ethnicities. Environmental factors may contribute to ethnic differences, but have not been well studied.

The Role of the Environment in Stroke

Studies have found links between both the physical and social environment and cardiovascular outcomes, such as the associations identified between air pollution and cardiovascular disease mortality^{48,49} and between neighborhood disadvantage and coronary heart disease incidence.⁵⁰ A schematic of potential mechanisms linking aspects of the physical and social environment to cardiovascular disease is shown in Figure 1.1 from Diez Roux.⁵¹ Both stroke and heart disease typically result from atherosclerosis with common risk factors such as diabetes, hypertension and hyperlipidemia. Because of the shared biology and risk factors, the pathways linking environments and ischemic stroke are likely similar to those for heart disease.

From a biologic perspective, environmental features could plausibly influence stroke risk and initial stroke severity. For example, both PM_{2.5} and O₃ are believed to act on the cardiovascular system through interrelated pathways of inflammation and autonomic balance. By initiating or accelerating atherosclerosis,⁵² leading to the generation of pro-thrombotic factors, or potentially triggering thrombosis, exposure to air pollutants could lead to elevated risk for acute stroke (Figure 1.2).⁵³ Severity may also be influenced by inflammation due to air pollutant exposure, as both C-reactive protein⁵⁴ and homocysteine⁵⁵ are associated with higher severity at hospital admission.

Links Between Air Pollution and Stroke

Studies have examined both chronic and acute exposure to air pollution as risk factors for stroke. Studies of acute exposures and stroke risk are more numerous than studies of chronic exposures, and acute changes in air pollution have been linked to increased risk of cardiovascular events.^{53,56–59} Less is known in terms of associations between air pollution exposures and stroke specifically. Currently, inconsistent evidence exists about whether acute exposure to air pollution increases stroke incidence^{10,11,60} or not,^{12,13,61} and whether air pollution is more strongly related to ischemic strokes than to hemorrhagic.^{10,11,60,62,63} Dominici et al. found a 1.24% increased risk of cerebrovascular disease with a 10µg/m³ increase in same-day PM_{2.5} (95% CI: 0.35-2.05) using a time-series study, but the findings were limited by reliance on hospital admissions data to identify strokes.⁶⁴ In contrast, Maheswaran et al. did not find associations, using an ecologic correlation study design, between outdoor air pollutants (modeled PM₁₀ and NO₂ concentrations) and ischemic stroke incidence using data from the South London Stroke Register (RR=1.14; 95% CI: 0.72-1.81 and RR=1.09; 95% CI: 0.91-1.30, respectively);¹² this study captured both acute and chronic exposure effects of air pollution that could not be disentangled. Henrotin et al.

used strokes identified from the Dijon Stroke Register to investigate whether air pollution was associated with stroke risk. They found, using a case-crossover design, that O₃ had a statistically significant association with increased ischemic stroke risk overall and among men, but not with hemorrhagic stroke. Further, they found that the impact of O₃ might be independent of PM in its association with stroke and that cardiovascular risk factors might increase the association between O₃ and stroke risk.¹¹ In a follow-up study with increased sample size, Henrotin et al. aimed to confirm the association between O₃ and ischemic strokes. In this study, they found a borderline association between O₃ and incident ischemic stroke (OR=1.041; 95% CI: 0.996-1.089).¹⁰ In contrast, O'Donnell et al. reported a negative association between PM_{2.5} and ischemic stroke risk also using a case-crossover design in Ontario, Canada (mean change: -0.7%, 95% CI: -6.3%-5.1%).¹³ The variation in these findings could be a function of the study designs, pollutant levels, geographical locations or demographic and clinical makeup of the populations. In addition, the time-series study design frequently used in these studies^{12,63,65-67} control for confounders in different ways, which may also lead to variability in findings.⁶⁸

Few studies in the US have looked at the relationship between air pollution and stroke, with only three, to our knowledge, utilizing the case-crossover design.^{14,69,70} A study from Alleghany County, Pennsylvania reported suggestive associations between O₃ and stroke hospitalizations, but restricted their analysis to individuals aged 65 years or older. Similarly, among Medicare beneficiaries, higher levels of PM₁₀ were associated with higher levels of hospital admissions in 9 US cities.⁶⁹ This early study lead to more refined classification of stroke onset time in future work, as using the date of hospitalization likely underestimates the strength of the air pollution-stroke association.⁷¹ Following up the 9 US cities study, Wellenius et al. used air pollution data from the greater Boston area and reported that an increase in PM_{2.5} in the 24

hours preceding stroke onset was associated with an 11% increase in the odds of ischemic stroke (95% CI: 1.03-1.20; IQR: 6.4 $\mu\text{g}/\text{m}^3$) after control for seasonality, time trends and time-invariant confounders.¹⁴ However, this study was limited by the fact that the strokes were not validated and a single monitoring site was used for exposure data. The greater Boston area is also predominantly white, which means that these results may not translate to more racially and ethnically diverse areas if differences in susceptibility by race-ethnicity exist.

Aside from studies focused on risk of incident stroke, only two studies have considered recurrent stroke as a specific endpoint.^{10,72} Considering recurrent stroke is important as those with a previous stroke may represent a group particularly vulnerable to the effects of air pollution.¹⁴ These case-crossover studies, both in France, found that short-term exposure to air pollution, specifically a lagged 8 hour average of O_3 levels, was associated with an increase in ischemic stroke recurrence.^{10,72} These studies were limited in that it was unclear when these recurrent strokes occurred in relation to the incident stroke event. Large variations in time to recurrence muddle the interpretation of the association between air pollution and risk as the risk of recurrence is greatest immediately following stroke and then dissipates over time.^{26,73} One of the studies also included transient ischemic attacks (TIA) in their definition of recurrent stroke,¹⁰ which could lead to uncertainty in the air pollution-recurrent ischemic stroke association if the association between air pollution and TIA is different from the association between air pollution and recurrent ischemic stroke.

Only two previous studies have examined the association between air pollution and initial stroke severity.^{15,16} Studies from the United Kingdom (long-term exposure)¹⁵ and Denmark (short-term exposure),¹⁶ both observed associations between higher exposure to air pollution and risk of stroke among those with mild but not severe stroke. These results were contrary to

expectations, but previous work has indicated that air pollution levels are associated with strokes characterized as large-artery atherosclerotic strokes, small-vessel occlusions, lacunar strokes, and TIAs rather than cardioembolic strokes,^{11,13,14,74} which may be consistent with an association with milder strokes.

Vulnerable Subgroups, Air pollution, and Stroke

Studies have found that exposure to air pollution affects groups with certain characteristics differently.^{19,75} For example, children and older adults may be “at-risk” populations for the health effects of air pollution.⁷⁶ With younger children’s lungs still developing and older adults having a higher prevalence of preexisting cardiovascular disease, these groups likely are more susceptible to the influence of air pollution.⁷⁵ While these vulnerable groups have been primarily identified with cardiovascular or respiratory endpoints, less is known about susceptible subgroups with stroke endpoints. Evidence for interactions between demographic factors and comorbid conditions and air pollution on stroke risk is growing. Those at older ages have stronger associations between air pollution and stroke risk than those at younger ages,⁷⁷ as do those with diabetes (compared to those without diabetes),¹³ and those that have more cardiovascular risk factors.¹⁰ Additional work is needed to understand who is most susceptible to the effects of air pollution on stroke.

Little work on air pollution has been conducted in diverse US populations even though the association between air pollution and stroke may vary by ethnicity due to differences in biological susceptibility or health conditions that cause enhanced vulnerability to air pollutants.^{19,75} Previous research has demonstrated that Hispanics may be more susceptible to PM-induced cardiovascular health effects⁷⁵ and stronger associations were found between PM_{2.5} and ischemic stroke in those with diabetes.¹³ Since MAs have an increased prevalence of

diabetes,^{78,79} the association between air pollution and stroke may be greater than that seen in NHWs. Additionally, because MAs are more likely to live in disadvantaged neighborhoods,⁸⁰ they likely experience a greater prevalence of air pollution exposure, which tends to cluster in more urban and disadvantaged areas, than their NHW counterparts.²⁰ These environments may also have an altered chemical composition of the pollution mixture,^{20,21} due to greater proximity to roadways or factories.^{20,81} While differences in exposure history are likely important, they cannot be easily assessed in acute exposure studies without personal monitors. Most acute population-level exposure studies in stroke use centralized air pollution monitoring, so one would be unable to determine if two individuals living in close proximity to one another had different histories of air pollution exposure.

The Role of Residential Neighborhoods on Stroke

There is a growing body of research considering the association between environmental factors and stroke risk by assessing socioeconomic disadvantage at the neighborhood level. The results are fairly consistent in showing that lower neighborhood SES is associated with stroke risk^{80,82-86} and mortality.^{87,88} However, little work has focused on how neighborhoods may contribute to stroke severity, which is an important predictor of stroke outcomes.³⁻⁷ Greater disadvantage was found to be associated with greater initial stroke severity in a bi-racial US community, with those in the poorest census tracts having a 2.23 point higher National Institutes of Health Stroke Scale (NIHSS) score compared to those in the richest census tracts (95% CI: 1.06-3.39).¹⁷ Further, the odds of severe stroke were twice as high for individuals living within the poorest compared to the richest census tracts (95% CI: 1.2-3.2). Similarly, in a Scottish study, a one point higher continuous neighborhood deprivation score was associated with a 0.26 point higher modified NIHSS score (95% CI: 0.00-0.53), with the association being stronger in

older patients (≥ 65 years of age; 0.45, 95% CI: 0.10-0.77).⁸⁹ The mechanisms linking neighborhood SES to stroke severity are unclear, but may include the influence of neighborhood features on risk factors for severe stroke,⁸⁹⁻⁹² neighborhood stressors, such as neighborhood violence and disorder, which may influence physiologic stress response,^{93,94} or an impact on other factors important to stroke severity, such as stroke awareness and hospital delay times.^{95,96} Neighborhood SES may also operate through the physical environment of these neighborhoods and air pollution, as previously described. More work is needed to understand the influence of neighborhoods on stroke severity.

The Synergistic Effects of Neighborhood SES and Air Pollution

Aspects of the social and physical environments may interact to influence stroke. A synergistic association between air pollution and neighborhood SES on cardiovascular mortality has been observed, with air pollution having greater effects on mortality in areas with lower neighborhood SES.⁹⁷⁻¹⁰⁰ Individuals residing in low SES neighborhoods or areas of greater neighborhood disadvantage experience more psychosocial stress and violence, which has been shown to increase susceptibility to air pollution for asthma via oxidative stress and inflammation,^{101,102} and may do so similarly for stroke as oxidative stress¹⁰³ and C-reactive protein influence stroke risk and severity.¹⁰⁴ Neighborhood stressors could also make individuals more susceptible to the influence of air pollution via reduced access to medications.¹⁹ Medications can treat and alleviate respiratory symptoms due to air pollution exposure and continued use of corticosteroids can lessen the inflammation response, possibly reducing the pro-inflammatory actions of air pollutants. Increased susceptibility to air pollution in low SES neighborhoods could also be due to nutritional deficits of the residents from lack of healthy food availability.¹⁸ Studies have shown that antioxidant vitamins and n-3 poly-unsaturated fatty acids

might protect against the adverse influences of air pollution,^{105–108} such that individuals with diets lacking in these nutrients may have increased susceptibility to the effects of air pollution. Evidence of a synergistic association between air pollution and neighborhood disadvantage on stroke severity would be important in terms of environmental justice; as those living in low income areas may continue to suffer the negative effects of air pollution disproportionately to those living in more affluent areas.¹⁰⁹

Previous Work in the Study Community

The current project focuses on the community from the BASIC Project which is based in Nueces County, Texas. BASIC is a longstanding stroke surveillance study which ascertains and validates all strokes in the study community. This coastal community is home to several refineries and chemical plants, with 19 of them identified in the years from 1997 to 2002.⁶⁵ In addition, this community is predominantly MA. The combination of a large number of point emission sources, a substantial minority population, and ongoing stroke surveillance provides an excellent opportunity to investigate air pollution and stroke risk and severity and whether MAs have enhanced susceptibility to the negative effects of air pollution relative to NHWs.

Previous work in this study community has demonstrated links between the environment and stroke and supports further study in this population. For example, in a time-series study in this community, Lisabeth et al. found borderline statistically significant associations between PM_{2.5} and O₃ and risk of ischemic stroke and TIA with a 3% increase in same-day risk (95% CI: 0.99-1.07) for PM_{2.5} and a 4% increase in risk (95% CI: 0.99-1.09) for previous-day O₃.⁶⁵ Additionally, investigators of this study considered the association between neighborhood-level disadvantage and ischemic stroke risk, concluding that low SES may influence stroke risk in certain subgroups (men, those under 75 years). They found that the effect of ethnicity was

attenuated after adjustment by a measure of neighborhood disadvantage suggesting that the environment may contribute to ethnic differences.⁸⁰ We build on this previous work by using a time-stratified case-crossover study design to investigate the association between air pollution and stroke. Additionally, by more than doubling the follow-up period, we improve our power to detect associations and are able to focus on a more specific endpoint of incident ischemic stroke using adjudicated stroke data that is not available in many other studies. We further expand this work by examining potential effect modification by ethnicity, looking at recurrent strokes, and investigating the influence of aspects of the environment on initial stroke severity.

1.4 Public Health Significance

Worldwide, 3.7 million deaths were attributable to ambient air pollution exposure with 40% through stroke.¹¹⁰ Essentially everyone is exposed to ambient air pollution and there is no safe level. Studies have shown that associations with health outcomes exist at air pollution levels that are below US EPA National Ambient Air Quality Standards (NAAQS) thresholds,^{14,65} and that it might be time to reevaluate these thresholds. If the governing bodies have the evidence to require lower emissions, the change happens nationally, and affects many at-risk individuals. Since stroke is the leading cause of disability in the US and is estimated to cost almost \$54 billion annually,^{1,2} even the small reduction in stroke incidence or recurrence due to lower air pollution levels has the potential to save lives and millions of dollars. For example, a 1% reduction in the number of new strokes per year could equate to lifetime savings of \$1.1 billion.²⁵ Additionally, evidence of a synergistic association between air pollution and neighborhood disadvantage on stroke severity would be important in terms of environmental justice; as those living in low income areas may continue to suffer the negative effects of air pollution disproportionately to those living in more affluent areas. This research could inform the

understanding of environmental risk factors for stroke incidence, recurrence and severity, which could suggest novel intervention targets to improve stroke outcomes.

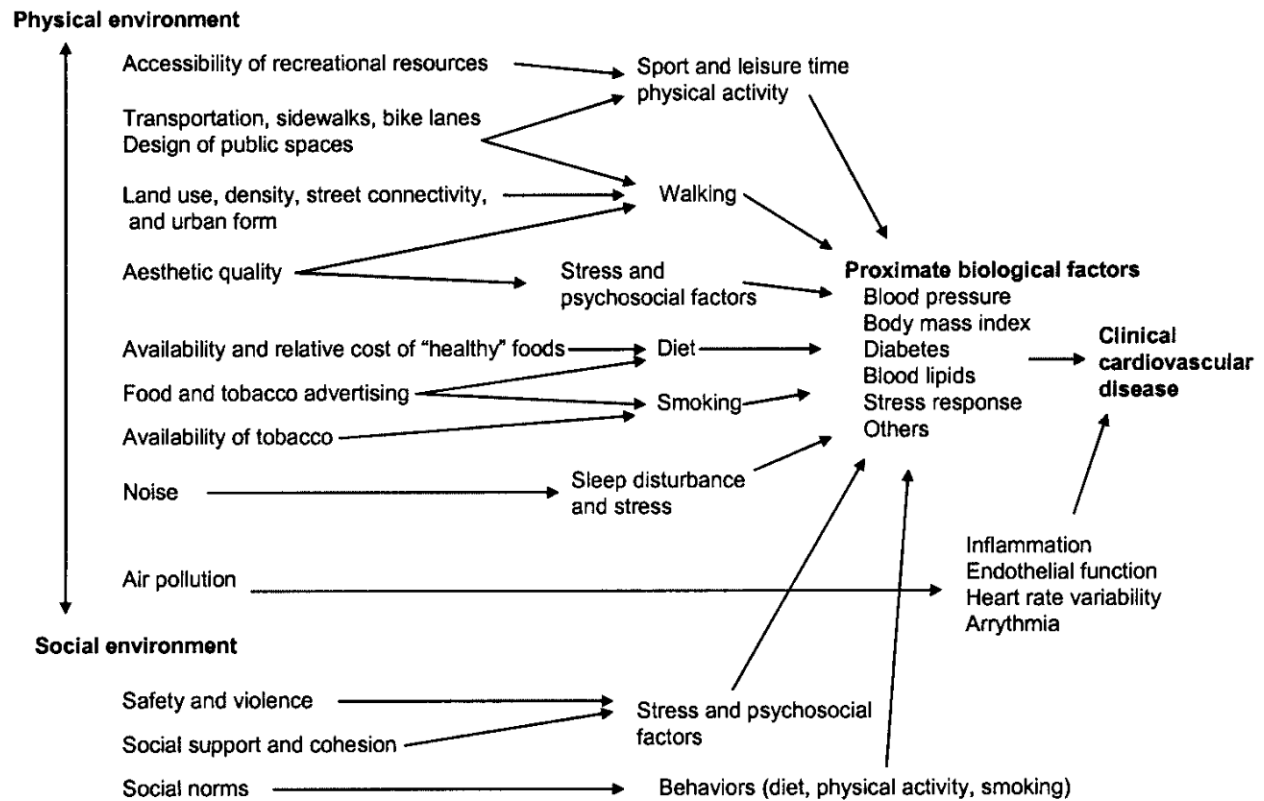


Figure 1.1 Schematic representation of possible pathways linking residential environments to cardiovascular risk.⁵¹

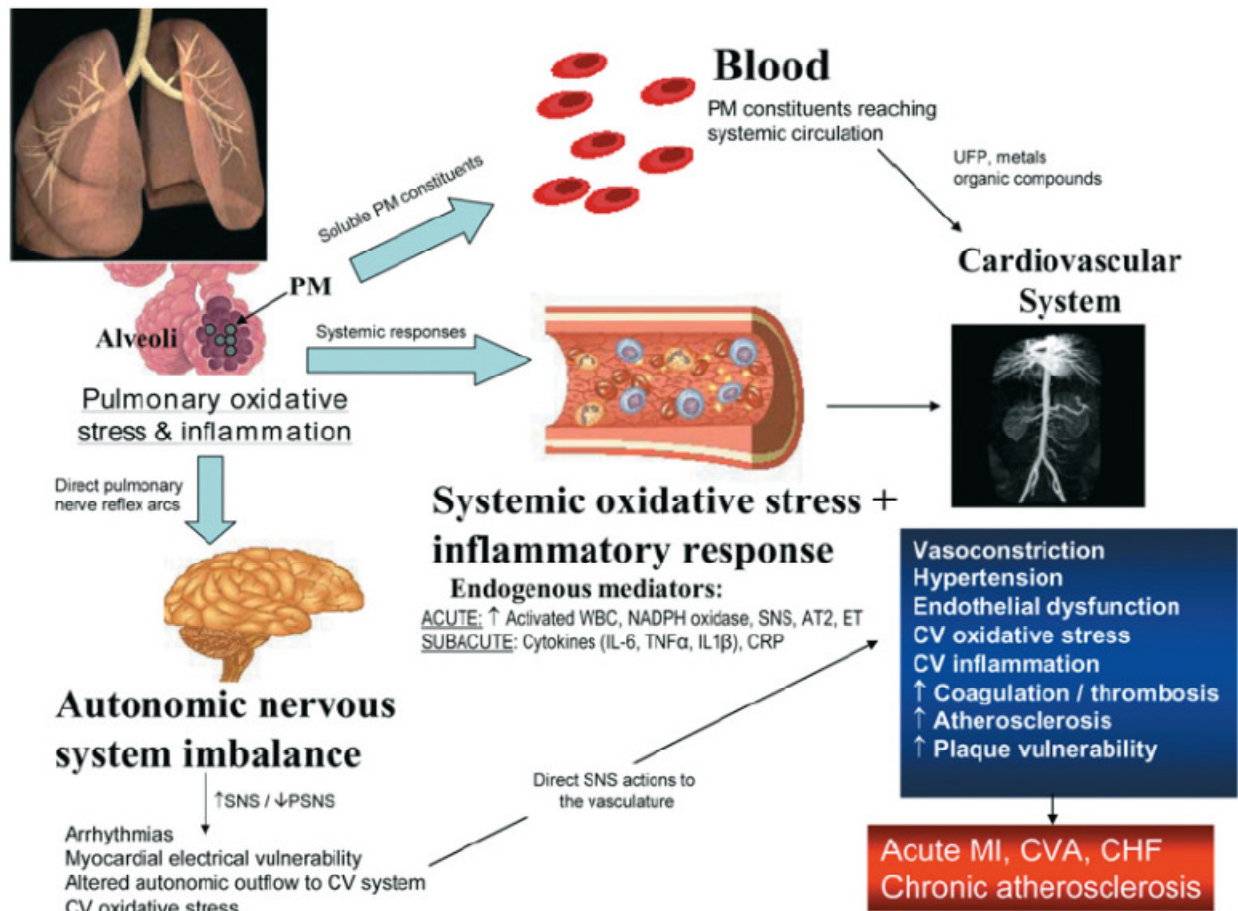


Figure 1.2 Broad biological pathways for how PM may cause cardiovascular events.⁵³

Chapter 2

Ethnic Differences in Short-Term Exposures to Ambient Air Pollution and Risk of Acute Ischemic Stroke

2.1 Introduction

Acute changes in air pollution have been linked to increased risk of cardiovascular events,^{53,56–59} but less is known in terms of the association with stroke specifically. Published studies of stroke have examined relationships with particulate matter than 2.5µm in aerodynamic diameter (PM_{2.5}) and ozone (O₃), but inconsistent evidence exists regarding the associations between acute exposures to these pollutants and stroke incidence.^{10–13} While some evidence suggests an association,¹⁴ this work has been conducted in a predominantly non-Hispanic white (NHW) population and cannot inform questions of enhanced susceptibility by race/ethnicity. Previous work in cardiovascular disease has reported differential associations by race/ethnicity, with Hispanics reported to be more susceptible to PM-induced health effects.⁷⁵ Greater short-term PM_{2.5} exposure was associated with an increased risk of cardiovascular mortality among Hispanics as compared to NHWs in a study of six California counties;¹¹¹ specifically, Hispanics had a 2.5-6% excess risk of mortality due to PM_{2.5} compared a 0-2% excess risk of mortality for NHWs. Similarly, the Multi-Ethnic Study of Atherosclerosis reported increases in PM_{2.5} among Hispanics were associated with a 22% elevated risk of coronary calcification,¹¹² while no increased risk was found in NHWs.

Our objective was to investigate associations between daily changes in ambient PM_{2.5} and O₃ levels and the risk of ischemic stroke and to explore effect modification by ethnicity among

individuals living in the bi-ethnic community of Nueces County, Texas between 2000 and 2012. Using a time-stratified case-crossover design, this analysis builds upon past research in this community that documented borderline significant associations between $PM_{2.5}$ and O_3 .⁶⁵ By more than doubling the follow-up period, we improve our power to detect associations and are able to focus on a more specific endpoint of ischemic stroke using adjudicated stroke data that is not available in many other studies. We furthermore add a new hypothesis that associations will be modified by ethnicity. Specifically, we hypothesized that increased levels of $PM_{2.5}$ and O_3 are associated with increased risk of incident ischemic stroke and that ethnicity modifies the associations between $PM_{2.5}$ and O_3 and incident ischemic stroke, such that the associations are greater in Mexican Americans (MA) compared with NHWs.

2.2 Methods

Study Population

Data are from the Brain Attack Surveillance in Corpus Christi (BASIC) project. BASIC is an ongoing population-based stroke surveillance study in Nueces County, Texas. Nueces County is located on the Gulf Coast, geographically isolated from the larger cities in southeast Texas, being over 150 miles from Houston and San Antonio making complete case capture for stroke possible. Approximately, 340,000 people live in Nueces County with the majority of the population (95%) residing in the urban city of Corpus Christi. Based on the 2010 Census, 61% of the population is MA and 33% is NHW.¹¹³

Study Design

We used a time-stratified case-crossover study design to assess the associations between air pollution ($PM_{2.5}$ and O_3) and odds of incident ischemic stroke and whether ethnicity modifies these associations. This study design allowed for the comparison of each subject's exposure to

air pollution prior to an acute stroke event with his or her own exposure during referent control periods where he/she did not have a stroke, effectively controlling for all time-invariant individual level characteristics.¹¹⁴ Control periods were selected on the same day of the week, falling in the same month as the stroke event. This selection approach avoids overlap bias and bias in time trends while controlling for seasonality and chronic confounders.¹¹⁵

Stroke Ascertainment

Methods for case identification in BASIC included active and passive surveillance techniques as has been previously described.^{116,117} Briefly, between January 1, 2000 and June 30, 2012, trained abstractors screened ischemic stroke cases from seven hospitals in the county. Out of hospital surveillance was also conducted using other sources (emergency departments, neurology offices, nursing homes, office of the medical examiner) at various times in the study as previously described.¹¹⁷ Admission logs and emergency department logs were screened daily for validated cerebrovascular diagnostic terms. Monthly admissions from the hospitals were also checked for cerebrovascular ICD-9 discharge codes for stroke. Study neurologists blinded to age and ethnicity validated strokes using source documentation according to criteria published by the MONICA (Multinational MONItoring of trends and determinants in Cardiovascular disease) project.¹¹⁸ Strokes were clinically defined as a focal neurologic deficit of acute onset specifically attributable to cerebrovascular distribution lasting longer than 24 hours. Date of first presentation of stroke was ascertained from the medical record. For the purposes of this study, we focused on first-ever completed ischemic strokes defined as no documented medical history of stroke/TIA in the medical record. Per the BASIC protocol, patients were excluded if they were younger than 45 years of age, lived outside of Nueces County, or if their strokes were traumatic.

Ethics Statement

The BASIC project was approved by the University of Michigan Institutional Review Board and each of the Nueces County hospital systems. A waiver of informed consent was approved for screening and identifying stroke patients and to abstract their charts. Study personnel screened hospital admission and discharge logs to identify patients who may have had a stroke. In addition, screening and abstraction was re-initiated at Corpus Christi neurology offices. Study personnel collected data from the medical record, made copies of specific forms in the medical record and sent to study neurologists for determination of stroke status.

Other Covariates Collected (Race/Ethnicity Ascertainment)

We ascertained race/ethnicity from medical records and race/ethnicity has been demonstrated to have a 97% agreement with self-reported race/ethnicity in this study community ($\kappa=0.94$).¹¹⁶ Additional information collected from medical records included demographics, traditional stroke risk factors, including diabetes, hypertension, atrial fibrillation, high cholesterol, heart disease, smoking status, and excessive alcohol use. Home addresses were recorded from the medical record and sent to an external company for geocoding.

Air Pollutant and Meteorology Data

We obtained air pollutant ($PM_{2.5}$ and O_3) and meteorological data for 2000 to 2012 from the Texas Commission on Environmental Quality's (TCEQ) Texas Air Monitoring Information System (TAMIS).²² Data for the air pollutants and wind direction were collected from one monitor centrally located within the urban population, *Corpus Christi West C4 (483550025)*. $PM_{2.5}$ was measured using a tapered element oscillating microbalance (TEOM) and O_3 was measured using an ultraviolet absorption analyzer. Relative humidity was calculated using dew point temperature from the National Oceanic and Atmospheric Administration (NOAA)^{23,119}

from the Corpus Christi International airport 6.5 km away from the pollutant monitor. PM_{2.5}, ambient temperature, and relative humidity were averaged daily (midnight to midnight) and the maximal 8-hour daily average was calculated for O₃.

Statistical Methods

We calculated descriptive statistics for the overall study population and by ethnicity. Chi-squared tests were used for categorical variables and Wilcoxon Rank Sum tests for continuous variables. We examined both air pollution and meteorological data with descriptive statistics as well as time-series plots. We used conditional logistic regression, stratifying on each stroke event, to calculate the odds ratios (ORs) and corresponding 95% confidence intervals associated with the air pollutant exposures. We assessed the functional forms of air pollutant and meteorological variables using categorical versions of continuous variables with levels defined by quartiles or by using penalized polynomial splines but found linear functional forms to be appropriate. All models included an individual air pollutant exposure and were adjusted for ambient temperature and relative humidity at the same lag as the pollutant. We calculated ORs for a 10 µg/m³ or 10 ppb change in PM_{2.5} and O₃, respectively. The association between each pollutant (either PM_{2.5} or O₃) and ischemic stroke was examined separately for exposures measured the same-day (lag 0), 1 day prior (lag 1), 2 days prior (lag 2), and 3 days prior (lag 3) to stroke onset. These lags were selected based on associations found in other studies, as well as the belief that this range includes the appropriate pathophysiologic window for triggering a stroke event.^{10,11,14,65} Day of the week and month were inherently adjusted for by the study design.¹¹⁴ We examined differential associations with air pollutant exposure by season by including an interaction term between temperature and air pollutant exposure in the model. We

added interaction terms to the models to test effect modification by ethnicity and reported ethnic-specific associations.

In secondary analyses, we explored the potential confounding effect of each pollutant with the other by running multi-pollutant models with both pollutants included. We conducted sensitivity analyses on the subset of cases with geocoded address that resided within five (5) kilometers (km) of the ambient monitor to test the robustness of the results to potential exposure measurement error. We similarly examined effect modification of the air pollution-stroke association by season (summer vs. non-summer) as well as a binary indicator for residing downwind of a pollution point source using daily prevailing wind direction.¹²⁰ Finally, we investigated if any differences in association by ethnicity could be explained by diabetes status by including an interaction term between diabetes status and air pollutant exposure in the ethnicity interaction models. We conducted all analyses using SAS version 9.3 (SAS Institute Inc, Cary, NC) and the R statistical package, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 Results

Of the 4,565 days in the study period, there were 105 days where there was insufficient hourly data to calculate the mean 24 hour PM_{2.5}, 224 days of missing PM_{2.5} data, one day with an unusually high average and peak PM_{2.5} (7.2% missing), and 106 days of missing O₃ data (2.3%) resulting in a total of 382 days excluded due to missingness of either air pollutant (8.4%). There were 2,948 ischemic strokes included in the analysis during the study period after 268 strokes were excluded due to missing exposure data. Median age of the stroke cases was 71 years (interquartile range (IQR): 59-80) (Table 2-1). Fifty-one percent of the stroke cases were women (n=1,511) and 56% were MA (n=1,652). MAs were more likely to have their strokes at younger

ages, have a history of diabetes, and have a history of hypertension, but less likely to be former smokers and have a history of atrial fibrillation. Most stroke cases (85%) resided within 20 km of the ambient monitoring site with a median distance of 6.9 km (IQR: 3.6-13.3). Median temperature for the study period was 23.3°C (IQR, 18.4-27.5) and median relative humidity was 78.3% (IQR: 70.2-84.0).

PM_{2.5}

The median pollutant level of PM_{2.5} for the study period was 7.7 µg/m³ (IQR: 5.7-10.6). Across all lags we found no association between the odds of incident ischemic stroke and PM_{2.5} concentrations (Figure 2.1). Effect modification of PM_{2.5} by ethnicity was, however, borderline significant for same-day PM_{2.5} levels (*p*-interaction=0.07). When stratified by ethnicity, we found that associations were consistently larger for MAs as compared to NHWs. These differences were most pronounced at lag 0 where a 10 µg/m³ higher same-day PM_{2.5} was associated with a 12% increase in the odds of an ischemic stroke in MAs (95% CI: 0.98-1.27) but a 7% decrease in the odds of an ischemic stroke in NHWs (95% CI: 0.80-1.08). Effect modification PM_{2.5} by ethnicity was weaker at other lag days.

O₃

The median pollutant level of O₃ for the study period was 35.7 ppb (IQR: 25.5-46.3). Across all individuals, O₃ levels were borderline significantly associated with the odds of incident ischemic stroke with the strongest associations for lags 1 and 2 (Figure 2.2). A 10 ppb higher lag 1 (or 2) O₃ was associated with a 2% increase in the odds of stroke (95% CI: 0.99-1.06). In models with interaction terms by ethnicity, NHWs were consistently found to have stronger relationships between O₃ and incident ischemic stroke with strongest differences at the longer lag periods. This ethnic modification was borderline significant for lag 2 O₃ levels (*p*-

interaction=0.06), but not other lags. For example, a 10 ppb higher lag 2 O₃, NHWs experienced a 6% increase in the odds of ischemic stroke (95% CI: 1.00-1.11) while MAs experienced no increase in odds (OR: 1.00, 95% CI: 0.92-1.05).

Sensitivity Analysis

Multi-pollutant models yielded similar results as reported for single pollutant models (Table 2-2). Results were similarly robust across season, presence of upwind pollution sources, and diabetes status. Restriction to the 1,121 ischemic strokes residing within five km of the air pollution monitor, increases in same-day PM_{2.5} and O₃ levels (from both single pollutant and multi-pollutant models) were also consistent with our main results, with slightly stronger associations for PM_{2.5} and slightly attenuated associations for O₃ (Table 2-3).

2.4 Discussion

In this population-based stroke study that included 13 years of validated ischemic strokes, we documented suggestive associations between higher short-term O₃ exposures and increased odds of incident ischemic stroke among NHWs but not MAs. No consistent associations were found for PM_{2.5}. These findings are in line with suggestive associations observed in this population over a 5-year follow-up period for O₃ and stroke, but not PM_{2.5}. This analysis added an additional 7 years of follow-up, restricted to validated incident ischemic stroke, and newly explored effect modification of associations between air pollution and stroke by ethnicity.

We hypothesized that both PM_{2.5} and O₃ would be associated with incident stroke risk, however the lack of overall associations found in our study is consistent with some previous studies. Studies from Canada with similar pollution levels also reported no association between ischemic stroke risk and PM_{2.5} in a case-crossover design.^{13,62} Case-crossover studies in Massachusetts,¹⁴ Pennsylvania,⁷⁰ and France¹⁰ reported no associations between same day or

previous day O₃ with risk of ischemic stroke; these studies also reported lower average daily concentrations of O₃ than we observed. Conversely to our results, some studies have found an association between PM_{2.5} and incident stroke. A study in Boston, MA found that an IQR increase in PM_{2.5} (6.4 µg/m³) in the 24 hours preceding stroke was associated with an OR of 1.11 (95% CI: 1.03-1.20) for ischemic stroke.¹⁴

Our results are consistent with a previous time-series study of this population over a shorter observation time (5 years), especially for O₃. In that study, we found borderline associations between risk of ischemic stroke/TIA and same-day PM_{2.5} (RR: 1.03; 95% CI: 0.99-1.07 and RR: 1.02; 95% CI: 0.97-1.08). Additional borderline associations were observed between risk of ischemic stroke/TIA and 1-day lag (RR: 1.03; 95% CI: 1.00-1.07 and RR: 1.04; 95% CI: 0.99-1.09) per IQR for PM_{2.5} (5.1 µg/m³) and O₃ (15.7 ppb), respectively. Although we hypothesized that associations would be stronger when restricted to incident ischemic stroke, it is possible that we did not observe associations in the same area over a longer time period because we excluded TIAs, which were included in the previous analysis and could have stronger associations with air pollutants than ischemic stroke,^{11,121} or may just improve statistical power. Another possible explanation may be that the observed levels of ambient air pollution in Nueces County were quite low, perhaps limiting our power to detect associations, even with the longer follow-up period. Our medians of 7.7 µg/m³ for PM_{2.5} and 35.7 ppb for O₃ were below the US EPA National Ambient Air Quality Standards (NAAQS) thresholds of 35.0 µg/m³ for daily PM_{2.5} and 75 ppb for fourth highest daily maximum 8-hour concentration for O₃.¹²²

A unique contribution of our investigation of air pollution and stroke was the consideration of differences by ethnicity. MAs have an increased stroke risk compared to NHWs,¹¹⁷ but the modification of relationships between stroke and air pollution have not been

investigated. *A priori*, we hypothesized a stronger association with PM_{2.5} in MAs based on previous research that has demonstrated that Hispanics are more susceptible to PM-induced cardiovascular health effects.⁷⁵ Although associations with PM_{2.5} were not strong in this study, the magnitude of the association we observed between PM_{2.5} and stroke in MAs for the same day lag was similar to or stronger than PM_{2.5} associations previously reported.^{14,65} Possible explanations for these differences may be that MAs have a higher prevalence of living in disadvantaged areas with different housing characteristics^{80,123} and hold more blue-collar occupations where they may have increased exposure to outdoor air pollution.¹²⁴ Another possibility is that biological impacts of air pollution on stroke risk may vary by ethnicity, in part due to increased prevalence of diabetes in MAs,^{78,79} as stronger associations have been found between PM_{2.5} and ischemic stroke among diabetics as compared to non-diabetics.¹³

In contrast, among NHWs, increases in lag 2 O₃ were associated with an increase in the odds of ischemic stroke, but not in MAs. The 6% increase in odds of ischemic stroke that we found for lag 2 exposure in NHWs was stronger than the results of Henrotin et al., who reported an OR of 1.04 for lag 2 O₃ exposure in a NHW European population.¹⁰ The reasons for these contrasting findings among PM_{2.5} and O₃ by ethnicity are not clear and could be due to differences in biologic susceptibility, differences in housing stock, differences in exposure history, or chance. Additional research is needed in diverse populations to investigate ethnic-specific effects.

There are some limitations of this work that warrant discussion. The classification of the exposure for individuals was limited by the fact that we only had one monitor in the study community. The measurements from the single fixed monitor may introduce measurement error into our analysis if the daily fluctuations were not homogeneous across the county. However,

another monitor in the county measuring 24 hour PM_{2.5} every three to six days using the Federal Reference Method showed large correlations ($\rho \geq 80\%$) with the single monitor used in our study. This is consistent with the topography of Nueces County (flat, with elevation varying from sea level to a maximum elevation of 180 feet¹²⁵) which suggests that air pollution exposures are likely to be highly correlated across space. We are also assuming that ambient pollutant concentrations are surrogates for personal pollutant exposures, which may be the case for PM_{2.5} but not O₃.¹²⁶ Another possibility is that air pollution exposures could have triggered other outcomes linked to these exposures such as myocardial infarction, intracerebral hemorrhage, or death such that competing risks would reduce the observed association between air pollution and incident stroke. A final issue is that we do not have the exact time of stroke onset, but rather the day of hospital presentation. Although consistent with much of the existing literature on air pollution and stroke, this may have resulted in an underestimation of the strength of the association between air pollution and ischemic stroke.⁷¹

In summary, we observed suggestive associations between higher PM_{2.5} and O₃ levels and incident ischemic stroke, with associations observed only among MAs for PM_{2.5} and only among NHWs for O₃. This study contributes to the literature by being the first study to our knowledge to address a possible ethnic difference in the influence of air pollution on stroke risk, and suggests that further study in diverse populations is warranted.

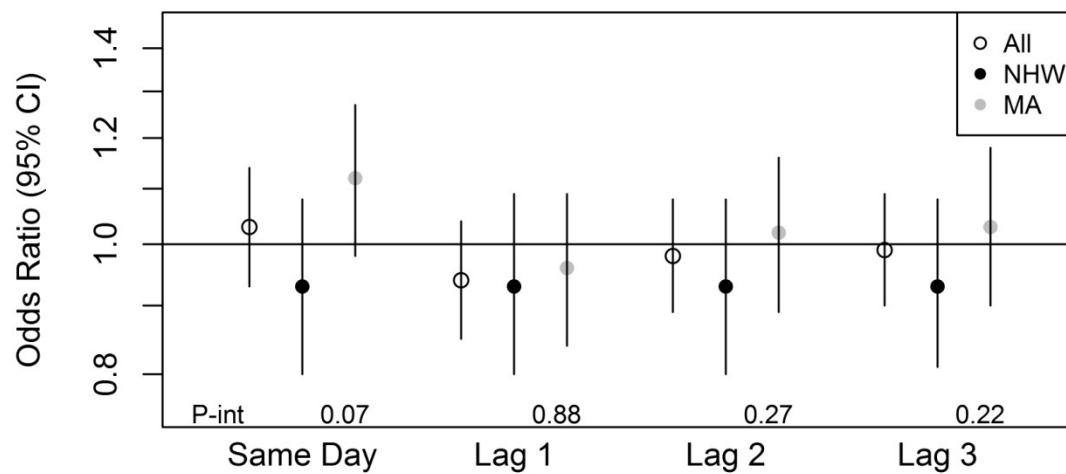


Figure 2.1 Odds ratios associated with a $10 \mu\text{g}/\text{m}^3$ increase in 24-hour $\text{PM}_{2.5}$ (particulate matter less than $2.5\mu\text{m}$ in diameter) overall and stratified by ethnicity for 2000-2012 incident ischemic stroke cases in Nueces County, Texas. Vertical bars indicate 95% confidence intervals. NHW corresponds to non-Hispanic White ethnicity, MA corresponds to Mexican American ethnicity, and P-int corresponds to the interaction p-value between ethnicity and $\text{PM}_{2.5}$.

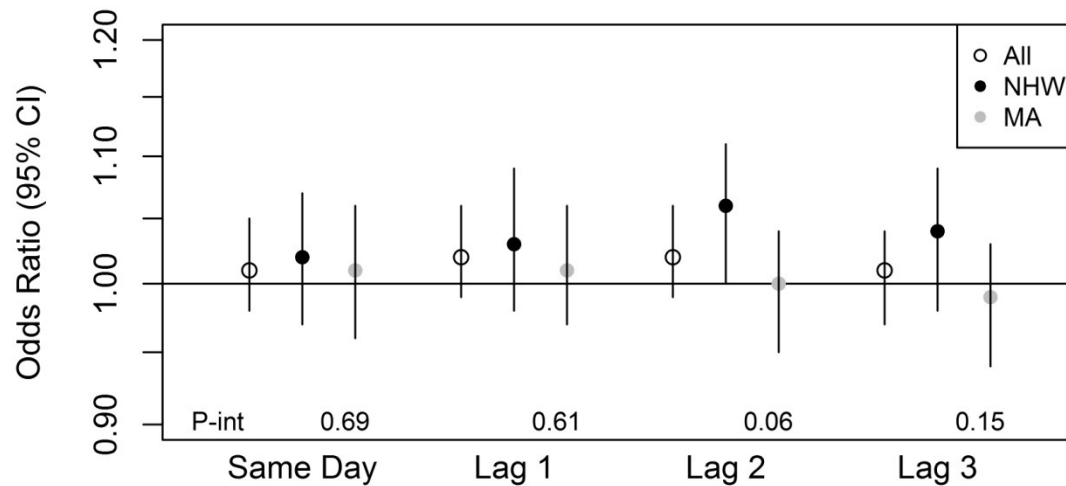


Figure 2.2 Odds ratios associated with a 10 ppb increase in maximal 8-hour O₃ (ozone) overall and stratified by ethnicity for 2000-2012 incident ischemic stroke cases in Nueces County, Texas. Vertical bars indicate 95% confidence intervals. NHW corresponds to non-Hispanic White ethnicity, MA corresponds to Mexican American ethnicity, and P-int corresponds to the interaction p-value between ethnicity and O₃.

Table 2-1 Characteristics of 2948 Incident Ischemic Strokes in Nueces County, Texas, 2000-2012.

Characteristic	Overall (N=2948)	MA (N=1652)	NHW (N=1296)	<i>P</i>
Age, median (Q1, Q3), y	71 (59, 80)	67 (57, 78)	75 (63, 83)	<0.001
Female	1511 (51.3)	835 (50.5)	676 (52.2)	0.384
MA	1652 (56.0)	-	-	
Medical History				
Atrial fibrillation	390 (13.2)	152 (9.2)	238 (18.4)	<0.001
Coronary artery disease	895 (30.4)	499 (30.2)	396 (30.6)	0.846
Diabetes mellitus	1204 (40.8)	882 (53.4)	322 (24.9)	<0.001
High cholesterol	956 (32.4)	551 (33.4)	405 (31.3)	0.226
Hypertension	2204 (74.8)	1275 (77.2)	929 (71.7)	<0.001
Excessive alcohol use	189 (6.4)	107 (6.5)	82 (6.3)	0.873
Smoking History				
Current	610 (20.7)	340 (20.6)	270 (20.8)	0.867
Former	366 (12.4)	158 (9.6)	208 (16.1)	<0.001

MA = Mexican American; NHW = Non-Hispanic White; Q = quartile.

Table 2-2 Single pollutant and dual pollutant overall models for a 10 µg/m³ or 10 ppb increase in PM_{2.5} or O₃, respectively.

	Single Pollutant	Multi- Pollutant*
	OR (95% CI)	OR (95% CI)
Mean 24hr PM_{2.5}		
No Lag	1.03 (0.93, 1.14)	1.03 (0.93, 1.13)
1 Day Lag	0.94 (0.85, 1.04)	0.93 (0.84, 1.03)
2 Day Lag	0.98 (0.89, 1.08)	0.97 (0.87, 1.07)
3 Day Lag	0.99 (0.90, 1.09)	0.98 (0.89, 1.09)
Max 8hr O₃		
No Lag	1.01 (0.98, 1.05)	1.01 (0.97, 1.05)
1 Day Lag	1.02 (0.99, 1.06)	1.03 (0.99, 1.06)
2 Day Lag	1.02 (0.99, 1.06)	1.02 (0.99, 1.06)
3 Day Lag	1.01 (0.97, 1.04)	1.01 (0.97, 1.05)

OR = odds ratio; CI = confidence interval; PM_{2.5} = particulate matter less than 2.5µm in diameter; O₃ = ozone.

*Multi-pollutant models include both PM_{2.5} and O₃ exposures

Table 2-3 Odds ratios associated with a 10 $\mu\text{g}/\text{m}^3$ or 10 ppb increase in $\text{PM}_{2.5}$ or O_3 , respectively, among those that reside within 5km of the air pollutant monitor overall and stratified by ethnicity for 2000-2012 incident ischemic stroke cases in Nueces County, Texas.

	Overall	MA	NHW	Interaction
	OR (95% CI)	OR (95% CI)	OR (95% CI)	P
Mean 24hr $\text{PM}_{2.5}$				
No Lag	1.11 (0.95, 1.28)	1.16 (0.98, 1.37)	0.95 (0.69, 1.31)	0.26
1 Day Lag	0.92 (0.79, 1.08)	0.95 (0.80, 1.14)	0.82 (0.58, 1.16)	0.58
2 Day Lag	0.91 (0.78, 1.07)	0.95 (0.79, 1.14)	0.81 (0.58, 1.13)	0.55
3 Day Lag	1.02 (0.87, 1.18)	1.02 (0.86, 1.21)	1.00 (0.72, 1.38)	0.95
Max 8hr O_3				
No Lag	1.02 (0.97, 1.08)	1.02 (0.96, 1.08)	1.04 (0.93, 1.16)	0.57
1 Day Lag	1.00 (0.95, 1.06)	0.98 (0.93, 1.05)	1.07 (0.96, 1.20)	0.44
2 Day Lag	0.98 (0.92, 1.03)	0.94 (0.88, 1.01)	1.08 (0.97, 1.20)	0.21
3 Day Lag	0.98 (0.93, 1.04)	0.95 (0.89, 1.01)	1.10 (0.98, 1.23)	0.45

OR = odds ratio; CI = confidence interval; $\text{PM}_{2.5}$ = particulate matter less than $2.5\mu\text{m}$ in diameter; NHW = non-Hispanic white; MA = Mexican American.

Chapter 3

Short-Term Exposures to Ambient Air Pollution and Risk of Recurrent Ischemic Stroke

3.1 Introduction

An estimated 795,000 people have a stroke each year, with 185,000 being recurrent events.²⁵ Estimates of the 1-year cumulative risk of recurrence range from 7 to 13%.^{9,26–31} Recurrent strokes are associated with worse outcomes and greater mortality relative to first strokes.^{32–35} Over the last century, stroke mortality has declined considerably resulting in an increasing population of stroke survivors who are at risk for multiple stroke events.³⁶ Projections suggest that by 2030 the number of stroke survivors will increase by 3.4 million from 2012, signifying stroke recurrence will take on increasing public health importance.³⁷

Short-term ambient air pollution as a risk factor for stroke has been gaining attention.^{10,13,14,65,127,128} Pollutants such as fine particulate matter less than 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$) and ozone (O_3) are believed to act on the cardiovascular system through interrelated pathways of inflammation and autonomic balance leading to vascular and hemodynamic changes, such as the generation of pro-thrombotic factors, potentially triggering thrombosis and leading to elevated stroke risk.^{53,129} Although associations between air pollution and risk of stroke have been observed, the evidence for short-term effects of air pollution on risk of stroke recurrence is in its infancy with only a few studies reported to date.^{10,14,72} While there is little evidence, it is plausible that individuals with prior stroke may be more vulnerable to the effects of air pollution on stroke given they are likely to have systemic or more severe atherosclerosis in the vessels of the brain.^{62,72} Recently, there has been a call by researchers to

further investigate the susceptibility of persons with a history of stroke to the effects of air pollution.¹³⁰

Different subgroups, based on sociodemographic characteristics and clinical factors, have been identified as more vulnerable to the effects of air pollution.^{19,75} These susceptible groups have also been specifically identified in stroke. For example, among those with diabetes, stronger associations have been found between PM_{2.5} and ischemic stroke,¹³ and between O₃ and recurrent ischemic stroke,⁷² compared to non-diabetics. Men and those without a history of atrial fibrillation (AF) have also been found to have positive associations between PM_{2.5} and ischemic stroke, compared to their counterparts (women and those with a history of AF, respectively).¹³ Additional susceptible subgroups have not been thoroughly investigated with respect to stroke recurrence.

Our objective was to investigate the association between daily variations in ambient air pollutant (PM_{2.5} and O₃) levels and risk of recurrent stroke. We used a time-stratified case-crossover design among individuals with ischemic stroke living in the bi-ethnic community of Nueces County, Texas between 2000 and 2012. We hypothesized that higher levels of PM_{2.5} and O₃ are associated with increased risk of recurrent stroke. Secondarily, we sought to identify whether these associations were modified by sociodemographic and clinical factors.

3.2 Methods

Study Population

Data are from the Brain Attack Surveillance in Corpus Christi (BASIC) Project, which is an ongoing population-based stroke surveillance study in Nueces County, Texas. Nueces County is located on the Gulf Coast, over 150 miles from Houston and San Antonio. This geographic isolation from the larger cities in southeast Texas makes complete case capture for stroke events

possible. Approximately, 340,000 people live in Nueces County with 61% of the population being MA and the majority of the population (95%) residing in the urban city of Corpus Christi.¹¹³

Study Design

A time-stratified case-crossover design was used to assess the association between air pollution and the odds of recurrent stroke among individuals with ischemic stroke and whether sociodemographic and clinical factors modify these associations. This study design effectively controls for all time-invariant individual level characteristics, while comparing each subject's exposure to air pollution prior to recurrent stroke event with his or her own exposure during referent control periods where he/she did not have a recurrent stroke.¹¹⁴ Control periods were selected on the same day of the week, falling in the same month as the recurrent stroke. This selection approach avoids overlap bias and bias in time trends while controlling for seasonality and chronic confounders.^{115,131}

Stroke Ascertainment

A combination of active and passive surveillance techniques were used to identify ischemic stroke cases between January 2000 and June 2012, as has been previously described.^{116,117} Active surveillance involved trained abstractors screening admission logs and emergency department logs daily for validated cerebrovascular diagnostic terms at seven hospitals in the county. Passive surveillance involved identification through monthly admissions from the hospitals checking for cerebrovascular discharge codes, using International Classification of Diseases, Ninth Revision (ICD-9) codes (430-438). Out of hospital surveillance was included from other sources (emergency departments, neurology offices, nursing homes, office of the medical examiner) at various times in the study as previously described.¹¹⁷ Study

neurologists blinded to age and ethnicity validated strokes using source documentation according to published criteria.¹¹⁸ Ischemic strokes were defined clinically as a focal neurologic deficit of acute onset specifically attributable to cerebrovascular distribution lasting longer than 24 hours. Recurrent strokes were defined as the first recurrent ischemic stroke (one per individual) following an incident ischemic stroke identified in BASIC. Recurrent strokes that occurred on the same day as the first stroke were excluded. Per the BASIC protocol, patients were excluded if they were younger than 45 years of age, lived outside of Nueces County, or if their strokes were the result of trauma. The BASIC project was approved by the University of Michigan Institutional Review Board and each of the Nueces County hospital systems.

Air Pollution and Meteorology Data

Data for PM_{2.5}, O₃ and meteorological data from 2000 to 2012 were obtained from the Texas Commission on Environmental Quality's Texas Air Monitoring Information System.²² Air pollutant concentrations, ambient temperature and wind direction were collected from one monitor centrally located within the urban population, *Corpus Christi West C4 (483550025)*. Both PM_{2.5} and O₃ were measured continuously using a tapered element oscillating microbalance or an ultraviolet absorption analyzer, respectively. PM_{2.5} was averaged daily (midnight to midnight) and O₃ was summarized as the maximal 8-hour average. Ambient temperature was summarized as the mean daily average in degrees Celsius. Relative humidity was calculated using dew point temperature from the Corpus Christi International airport 6.5 km away through the National Oceanic and Atmospheric Administration (NOAA),^{23,119} and summarized as the average percent per day. Each air pollutant was examined on the day prior to recurrent stroke onset (a 1-day lag) based on associations from other studies and the belief that this time window includes the appropriate window for triggering a recurrent stroke.^{10,14,72}

Covariates

Individual level time-invariant features are controlled for by the time-stratified case-crossover design,¹¹⁴ however, these features can be investigated as effect modifiers.

Race/ethnicity was ascertained from medical records and has been demonstrated to have a 97% agreement with self-reported race/ethnicity in the study community (kappa=0.94).¹¹⁶

Demographics, smoking status, insurance status, traditional stroke risk factors, including diabetes, hypertension, atrial fibrillation (AF), and coronary artery disease (CAD), National Institutes of Health Stroke Scale (NIHSS) score of the index stroke, hospital discharge status of index stroke (discharged home versus not discharged home), and time since index stroke, were additionally collected from medical records. The NIHSS score was retrospectively calculated from data abstracted from the medical record in accordance with a validated method¹³² or directly abstracted. Home addresses at the time of the recurrent stroke were recorded from the medical record and sent to an external company for geocoding. Distance from air pollution monitor was calculated from the geocoded home address.

Statistical Methods

Descriptive statistics were calculated for the study population, air pollution exposures and meteorological data. Continuous variables were summarized using means or medians and categorical variables were summarized using frequencies and percents. Conditional logistic regression models, stratifying on each recurrent stroke, were used to calculate odds ratios (ORs) for a 10 $\mu\text{g}/\text{m}^3$ or 10 ppb change in previous-day $\text{PM}_{2.5}$ or O_3 , respectively, and corresponding 95% confidence intervals (CI). Conditional logistic models allow for the matched nature of the case-crossover design.¹³³ All models were adjusted for ambient temperature and relative humidity measured on the same day as pollutant exposure. Quartiles or penalized polynomial

splines were used to assess functional forms of air pollutants and meteorological variables. Linear functional forms were found to be appropriate for both air pollutant exposures as well as both meteorological variables. The association between each pollutant and recurrent stroke was first examined separately. Co-pollutant models with both air pollutants included were then examined to explore the potential confounding effects.

We examined whether the associations between concentrations of each pollutant and recurrent ischemic stroke differed by potential effect modifiers (i.e. susceptible subgroups) using fully stratified models. A χ^2 tests of homogeneity was performed to examine whether the associations were different across strata of the potential modifiers.¹³⁴ We examined age, sex, race/ethnicity, AF, CAD, diabetes, and hypertension as possible effect modifiers as these factors have been previously associated with enhanced susceptibility to the effects of air pollution.⁷⁵ In addition, we explored effect modification by smoking status, index stroke severity (initial NIHSS score), time since index stroke (within 90 days or within 1 year), and factors that could influence air pollution exposure (having been discharged home from the hospital).

Sensitivity analyses were conducted to investigate the robustness of our findings on different air pollution exposure days. The main analysis was repeated for same-day, 2 days prior and 3 days prior levels of PM_{2.5} and O₃. We also investigated whether distance from the air pollution monitor influenced the results by repeating the main analysis in the subset of cases that resided within five (5) kilometers (km) of the ambient monitor. All analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC) and the R statistical package, version 3.0.1.

3.3 Results

A total of 3,216 first-ever ischemic strokes were identified between January 1, 2000 and June 30, 2012 among NHWs and MAs; 388 of these individuals had a recurrent stroke.

Restricting to the first recurrent ischemic stroke and excluding those events that occurred on the same day as the index stroke, reduced our sample to 358. Our final analytic sample was 317 recurrent ischemic strokes after excluding 41 strokes that occurred on days with missing air pollution data (missing either PM_{2.5} or O₃). The mean age of the 317 recurrent stroke cases was 72 years (SD=12) (Table 3-1). Sixty-four percent of cases were MA (n=202) and 53% (n=169) were female. The median time to stroke recurrence was 1.1 years with an interquartile range (IQR) of 0.2 to 2.8 years and median length of follow up was 5.5 years (IQR: 2.2 to 9.0). The median levels of PM_{2.5} and O₃ over the study period were 7.7 µg/m³ (IQR: 5.6 to 10.7 µg/m³) and 35.2 ppb (IQR: 25.0 to 46.1 ppb), respectively.

We observed no associations between previous-day PM_{2.5} and O₃ and the odds of recurrent ischemic stroke (OR=0.95 per 10 µg/m³ of PM_{2.5}, 95% CI: 0.71 to 1.28 and OR=0.97 per 10 ppb of O₃, 95% CI: 0.87 to 1.07) after adjusting for ambient temperature, and relative humidity. After co-adjustment of both pollutants the results did not change for PM_{2.5} (OR=0.97, 95% CI: 0.72 to 1.31) or O₃ (OR=0.97, 95% CI: 0.87 to 1.08).

Figure 3.1 and Figure 3.2 display the results of the previous-day PM_{2.5} and O₃ stratified models, respectively. We did not find strong evidence of effect modification of the air pollution and recurrent stroke associations by sociodemographic and clinical factors with a few exceptions. The association between PM_{2.5} and recurrence was different between strata of CAD (p=0.04), with the associations being in opposite directions. Individuals who had a history of CAD had greater odds of having a recurrent stroke for a 10 µg/m³ higher previous-day PM_{2.5} (OR: 1.47; 95% CI: 0.91 to 2.40) relative to those without a history of CAD (OR: 0.76; 95% CI: 0.52 to 1.11). We also observed borderline evidence of effect modification of the O₃-recurrence association by history of AF (p=0.09) and time since index stroke (1 year, p=0.08). The

association among individuals who had a history of AF was borderline protective (OR=0.80 per 10 ppb, 95% CI: 0.62 to 1.02), while there was no association (OR=1.01, 95% CI: 0.90 to 1.14) among those without a history of AF. Among those that had their recurrent stroke within 1 year of their index stroke, the association between O₃ and recurrence was borderline protective (OR=0.87, 95% CI: 0.75 to 1.01), but the association among those with time since index stroke longer than 1 year was on the opposite side of the null (OR=1.06, 95% CI: 0.91 to 1.22).

Sensitivity analyses

Associations between air pollutants and recurrent stroke were consistently null for other lagged exposure days (lag 2 and lag 3 days), but there was a suggestive protective effect for same-day levels of both pollutants (Table 3-2). The results also did not differ by distance from the air pollution monitor for either PM_{2.5} or O₃ (results not shown).

3.4 Discussion

We observed no significant associations between previous-day levels of PM_{2.5} and O₃ and recurrent ischemic stroke in our population-based stroke surveillance study with 13 years of validated recurrent strokes. By using a time-stratified case-crossover design our findings are robust to confounding by individual-level characteristics and we were able to investigate effect modification of the air pollution-recurrent stroke association to identify susceptible subgroups. While we did not observe effect modification consistently across the two pollutants, some modifications were suggested.

Previous case-crossover studies have reported associations between higher levels of ambient air pollution and risk of recurrent stroke,^{10,14,72,130} however, these studies differed from ours in their selection of cases which may help to explain the differences in findings. Studies in Sweden and Boston, Massachusetts reported associations between stroke and PM (PM₁₀ and

PM_{2.5}) levels among those with a history of stroke,^{14,130} while French studies^{10,72} reported associations between lagged O₃ levels and odds of recurrent stroke. However, some of these studies included TIAs in their histories of ischemic stroke^{10,14} and also in their definition of recurrent strokes¹⁰ while we excluded TIAs. The biggest advantage to including TIAs in a study would be the increase in the number of subjects and thus statistical power. However, this advantage may be outweighed by the uncertainty of the association between air pollution and TIA. Although the number of recurrent strokes in our study was similar to previous studies,^{10,72} we may have been underpowered to detect an association, perhaps due to the fact that the observed levels of ambient air pollution in our study population were quite low.

Evidence has shown that the risk of recurrence is greatest immediately following stroke and that risk dissipates over time.^{26,73} Although we observed no significant effect modification for time since index stroke, stronger effects between PM_{2.5} and recurrence were suggested within 90 days of the first stroke event and yet inexplicably protective within one year for the association between O₃ and recurrence. Our findings in combination with what is known about risk of recurrent stroke suggests that time since the first stroke should be carefully considered in future studies. We observed only 86 strokes within 90 days, which limits our inference, but these trends warrant future consideration. Other large registries or surveillance studies would have the power to examine this question further. Pooling data across sites and using more advanced techniques for modeling exposure could improve the ability of such a study to investigate the association between air pollution exposures and risk of early recurrence.

Although we did not find strong differences in susceptibility by sociodemographic and clinical factors, we did find the suggestion of differences by history of CAD and AF. Those with CAD had an increased odds of recurrent stroke with higher levels of PM_{2.5} in contrast to those

without CAD, while those with AF had a decreased odds of recurrent stroke with higher levels of O₃ in contrast to those without AF. These findings should be interpreted with caution given our multiple tests and the fact that the stratum specific estimates were on opposing sides of the null. Nonetheless, supporting the finding of increased vulnerability among those with CAD, previous studies have demonstrated that those with CAD are more susceptible to the influence of PM_{2.5} on acute coronary events¹³⁵ and cardiovascular mortality.¹³⁶ Individuals with CAD are more likely to have large artery atherosclerosis than those without CAD.¹³⁷ Wellenius et al. examined the relation between PM_{2.5} and ischemic stroke subtype and reported that PM_{2.5} levels were associated with large artery strokes but not with cardioembolic strokes.¹⁴ Those with large-vessel atherothrombotic stroke have higher rates of stroke recurrence compared to other stroke subtypes suggesting that increased susceptibility in those with CAD may be due to their underlying atherosclerosis and stroke mechanism.¹³⁸ We did not have data on ischemic stroke subtype to further investigate this hypothesis.

The protective finding between O₃ and recurrence among those with AF is peculiar. Those with AF are older and more likely to have a more severe stroke,¹³⁹ so these stroke survivors may be less likely to go outside on hot days where O₃ levels are typically higher.¹⁴⁰ Indoor O₃ concentrations are less correlated with outdoor concentrations, especially with the use of air conditioning.¹⁴¹ Another possible explanation could be due to medication, as Warfarin dose and international normalized ratio (INR) are a moving target.¹⁴² If there were differences in medication effectiveness across pollution/temperature days, this could explain part of the protective association. It is unclear why we did not observe similar associations between PM_{2.5} and O₃, however, these exposures were not highly correlated ($p < 10\%$) on the study days.

There are some limitations that warrant discussion. In our study we have averaged daily exposure levels at a single monitoring station, which could result in exposure misclassification. However, we have found high correlations ($\rho \geq 80\%$) between multiple monitoring stations in the county and restricting our analyses to persons living within 5 km of a monitor did not alter our results. It is possible that this population of recurrent stroke subjects was more likely to be indoors in air conditioned environments.¹⁴³ This could reduce the correlations between personal exposures and ambient pollution levels. Given that the error in the exposure level should be independent of whether it was a case or a control day, we would anticipate bias towards the null. Another possible issue is that we may have some misclassification in the timing of our outcome given that we do not have the time of stroke onset, but rather the day of hospital presentation.⁷¹ Selection bias could also have played a role in our ability to detect an association between air pollution and recurrent stroke. In order to be included in our analysis, an individual must have survived their first ischemic stroke so this may be a population at lowered susceptibility to the effects of air pollution. Another possibility is that air pollution exposures could have triggered other outcomes linked to these exposures such as myocardial infarction, intracerebral hemorrhage, or death such that competing risks would reduce the observed association between air pollution and recurrent stroke.

In conclusion, we observed no associations between previous-day air pollution levels and recurrent ischemic stroke. Little work has been done to explore the influence of air pollutants on risk of recurrence, and more research is necessary in studies that are adequately powered to consider early recurrent stroke risk.

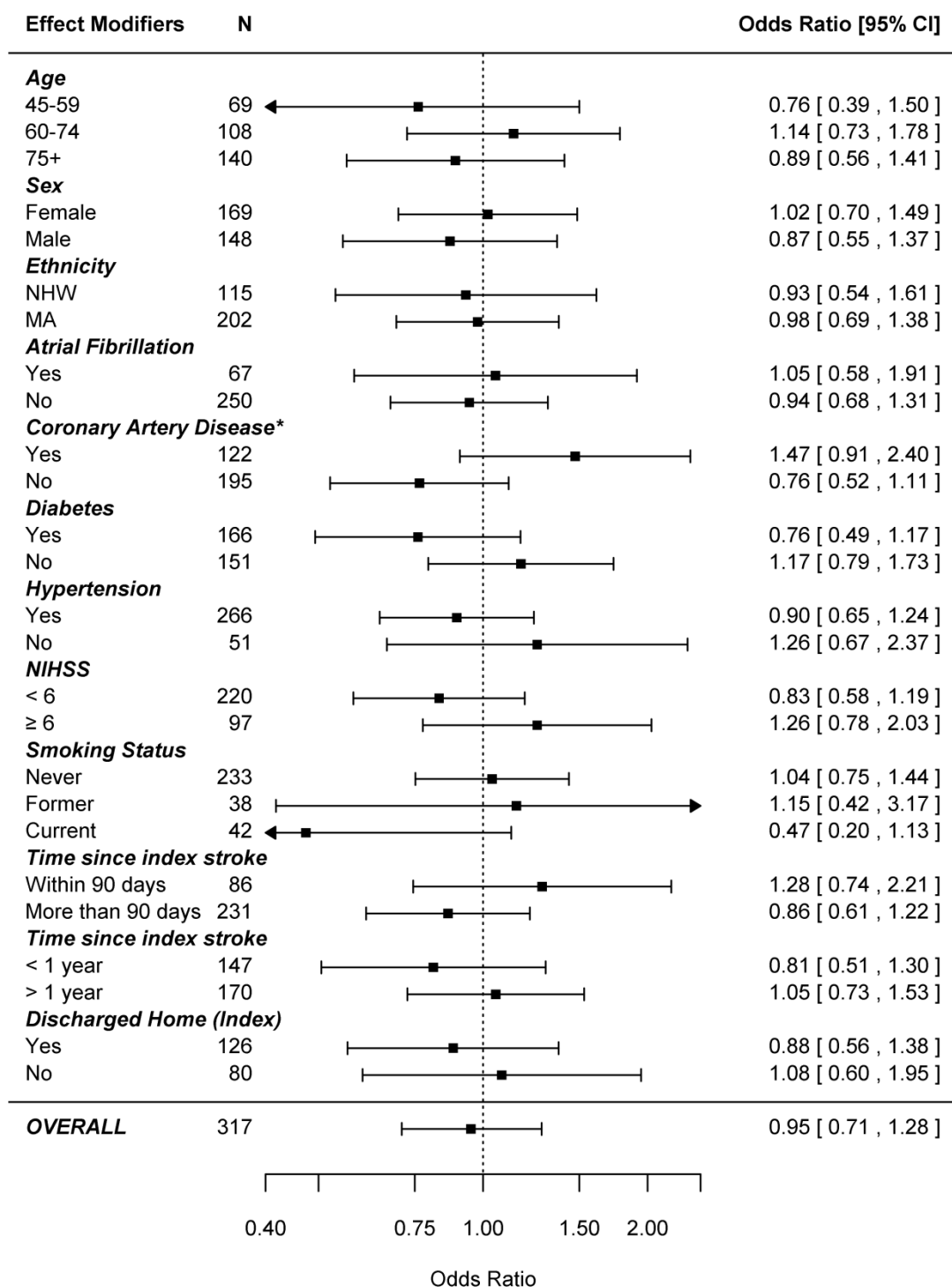


Figure 3.1 Odds ratios associated with a 10 $\mu\text{g}/\text{m}^3$ higher previous-day $\text{PM}_{2.5}$ (particulate matter less than $2.5\mu\text{m}$ in diameter) stratified by subgroups for 2000-2012 recurrent ischemic stroke cases in Nueces County, Texas. Bars indicate 95% confidence intervals. An asterisk (*) indicates a χ^2 test of homogeneity p-value < 0.10. NHW = Non-Hispanic white; MA = Mexican American; NIHSS = National Institute of Health Stroke Scale.

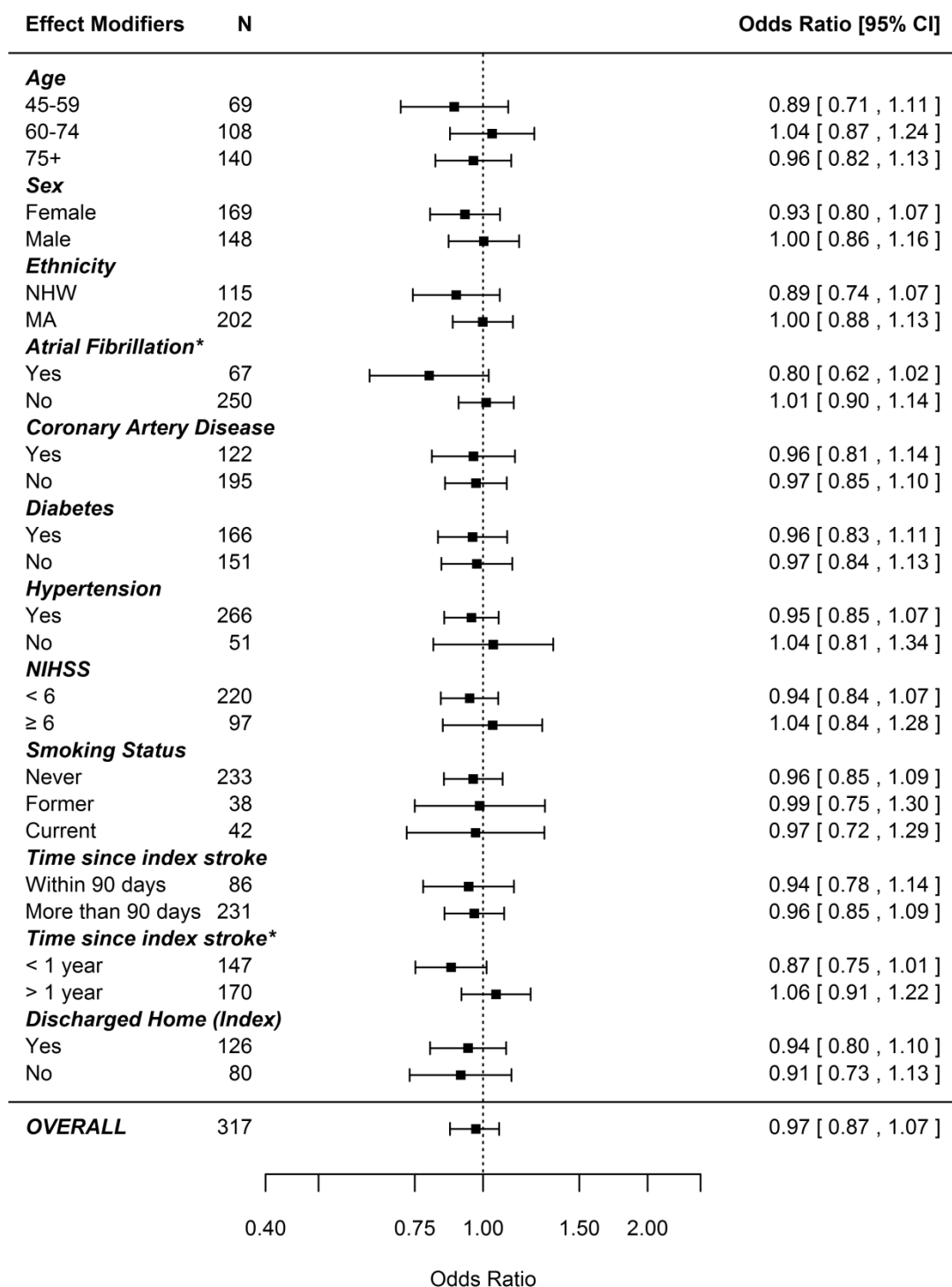


Figure 3.2 Odds ratios associated with a 10 ppb higher previous-day O₃ (ozone) stratified by subgroups for 2000-2012 recurrent ischemic stroke cases in Nueces County, Texas. Bars indicate 95% confidence intervals. An asterisk (*) indicates a χ^2 test of homogeneity p-value < 0.10. NHW = Non-Hispanic white; MA = Mexican American; NIHSS = National Institute of Health Stroke Scale.

Table 3-1 Characteristics (N (%)) for recurrent ischemic strokes between January 2000 and June 2012.

Characteristic	n=317
Age Group	
45-59	69 (22)
60-74	108 (34)
75+	140 (44)
Sex	
Female	169 (53)
Male	148 (47)
Ethnicity	
NHW	115 (36)
MA	202 (64)
Atrial Fibrillation	67 (21)
Coronary Artery Disease	122 (38)
Diabetes	166 (52)
Hypertension	266 (84)
NIHSS (Index)	
≥ 6	97 (31)
< 6	220 (69)
Smoking Status	
Never	233 (74)
Former	38 (12)
Current	42 (13)
Within 1 yr of index stroke	147 (46)
Within 5km of monitor	154 (48)
Within 90 days of index stroke	86 (27)
Discharged Home (Index) [†]	
Yes	126 (61)
No	80 (39)

NHW = Non-Hispanic white; MA = Mexican American; NIHSS = National Institute of Health Stroke Scale.

[†] Only available for a subset of the cases

Table 3-2 Odds ratios associated with a 10 $\mu\text{g}/\text{m}^3$ or 10 ppb higher previous-day $\text{PM}_{2.5}$ or O_3 , respectively, for 2000-2012 recurrent ischemic stroke cases in Nueces County, Texas.

Exposure	Mean 24hr $\text{PM}_{2.5}$		Max 8hr O_3	
	OR (CI)	P	OR (CI)	P
No Lag	0.73 (0.52, 1.01)	0.06	0.92 (0.83, 1.03)	0.08
1 Day Lag	0.95 (0.71, 1.28)	0.75	0.97 (0.87, 1.07)	0.88
2 Day Lag	0.93 (0.69, 1.24)	0.62	1.03 (0.92, 1.14)	0.90
3 Day Lag	0.90 (0.66, 1.23)	0.50	0.99 (0.89, 1.10)	0.95

$\text{PM}_{2.5}$ = particulate matter less than $2.5\mu\text{m}$ in diameter; O_3 = ozone; OR = odds ratio; CI = confidence interval; NHW = non-Hispanic white; MA = Mexican American.

Chapter 4

Synergistic Effects of Short-Term Air Pollution Exposures and Neighborhood

Disadvantage on Initial Stroke Severity

4.1 Introduction

Stroke is a leading cause of disability and is estimated to cost almost \$54 billion annually, in the United States,^{1,2} with severe strokes costing as much as two times that of mild strokes in acute hospital settings.²⁴ Initial stroke severity is an important predictor of post-stroke outcomes, including functional outcomes³⁻⁶ and mortality.⁷ Individual-level characteristics, such as age, atrial fibrillation, and cigarette smoking, are associated with stroke severity,¹³⁹ but the role of environmental influences is poorly understood.

Residential environments, including neighborhood socioeconomic status (SES), have been linked to stroke risk^{80,84,85,144-146} and survival.^{87,88} However, little work has focused on how neighborhoods may contribute to stroke severity. Neighborhood feelings of safety or social cohesion can lead to stress,^{93,94} which may alter endothelial function¹⁴⁷ and inflammation,¹⁴⁸ that in turn could influence severity.¹⁴⁹ Kleindorfer et al. found that greater neighborhood disadvantage was associated with greater initial stroke severity in a biracial US community.¹⁷ In a Scottish study, patients living in areas of greater deprivation had greater stroke severity, with the association being stronger in older patients (≥ 65 years of age).⁸⁹ These findings suggest that characteristics of residential environments may be associated with stroke severity but offer little explanation of the key environmental features that may explain such associations.

Exposures to air pollution may be one contributor to associations between neighborhood disadvantage and stroke severity. Air pollution has been repeatedly linked to cardiovascular events^{53,129} and disadvantaged communities often experience higher concentrations of air pollution from highways, power plants, and industrial sites.²⁰ Yet only two previous studies have examined the association between air pollution and initial stroke severity and their results were contrary to expectations.^{15,16} These studies from the United Kingdom¹⁵ and Denmark,¹⁶ observed associations between higher exposure to particulate matter less than 10 μm in aerodynamic diameter and risk of stroke among those with mild but not severe stroke. Neither study, however, examined the potential for synergism between air pollution and other characteristics of the neighborhood environment.

Evidence of synergism between air pollution and low neighborhood SES has been observed in several studies on cardiovascular mortality.^{97–100} Residing in a low SES neighborhood may act as a chronic stressor and make individuals more susceptible to the influence of air pollution via lack of healthy foods,¹⁸ reduced access to medications,¹⁹ altered chemical composition of the pollution mixture being more toxic via proximity to roadways, factories, or increased exposure to indoor pollutants,^{20,21} or other pathways. Evidence of a synergistic association between air pollution and neighborhood disadvantage on stroke severity would be important in terms of environmental justice, as those living in low income areas may continue to suffer the negative effects of air pollution disproportionately to those living in more affluent areas.

The objectives of this study were to investigate the effects of neighborhood disadvantage and air pollutants (particulate matter of aerodynamic diameter less than 2.5 μm (PM_{2.5}) and ozone (O₃)) on initial stroke severity in a population-based stroke surveillance study. We further

investigated possible synergism between these two exposures. We hypothesized that (1) higher levels of neighborhood disadvantage and air pollutants are associated with greater initial stroke severity and (2) associations between air pollutants and initial stroke severity are greater in more disadvantaged neighborhoods compared to less disadvantaged neighborhoods.

4.2 Methods

Stroke Identification and Classification

We identified incident ischemic stroke cases from the Brain Attack Surveillance in Corpus Christi (BASIC) project between January 2000 and June 2012. BASIC is an ongoing population-based stroke surveillance study in Nueces County, Texas. Nueces County is geographically isolated from the larger cities in southeast Texas, being over 150 miles from Houston and San Antonio making complete case capture for stroke possible. Based on the 2010 Census, approximately 340,000 people live in Nueces County with the majority of the population (95%) residing in the urban city of Corpus Christi.¹¹³

Methods for stroke identification in BASIC have been previously described.^{116,117} Briefly, active and passive surveillance techniques were utilized; trained abstractors screened ischemic stroke cases from seven hospitals in the county. Other sources (emergency departments, neurology offices, nursing homes, office of the medical examiner) were part of out of hospital surveillance which was conducted at various times in the study as previously described.¹¹⁷ Both admission logs and emergency department logs were screened for validated cerebrovascular diagnostic terms and monthly admissions from the hospitals were also checked for cerebrovascular ICD-9 discharge codes. Strokes were validated by study neurologists who were blinded to age and ethnicity, using source documentation according to criteria published by the MONICA (Multinational MONItoring of trends and determinants in Cardiovascular disease)

project.¹¹⁸ Strokes were clinically defined as a focal neurologic deficit of acute onset specifically attributable to cerebrovascular distribution lasting longer than 24 hours. Date of first presentation of stroke was ascertained from the medical record. Patients were excluded if they were younger than 45 years of age, lived outside of Nueces County, or if their strokes were the result of trauma. For the purposes of this study, we focused on first-ever completed ischemic strokes, defined as no documented history of stroke/TIA in the medical record.

Initial stroke severity, measured as the National Institutes of Health Stroke Scale (NIHSS) score, was abstracted from the medical record or retrospectively calculated from the medical record using a validated method.¹³² Severe stroke was defined as an NIHSS score ≥ 7 based on the upper quartile of the NIHSS distribution. We ascertained additional information from medical records including demographics (age, sex, race/ethnicity) and traditional stroke risk factors, including atrial fibrillation, coronary artery disease, diabetes, hypertension, and smoking status. Home addresses were recorded from the medical record and sent to an external company for geocoding.

Neighborhood Disadvantage Score

Census tracts were used as proxies for neighborhoods and stroke cases were assigned to the census track where they resided at the time of stroke. We identified 12 neighborhood-level census variables that reflected sociodemographic domains of race/ethnicity and wealth/income from the 2000 Census, American Community Survey 2005-2009 and American Community Survey 2007-2011 including: percent non-Hispanic white, Hispanic, with more than high school education, with more than a bachelor degree, below poverty, unemployed, with managerial occupation, with income at least \$50,000, with interest, dividend, or rental income, with household with no telephone, with household with no vehicle maintained, and median household

income. Following the work of previous studies,^{80,150} we created a composite score for neighborhood disadvantage based on z-scores for the individual neighborhood-level Census variables; variables were reverse coded as necessary, such that positive z-scores would represent higher neighborhood disadvantage. These scores were then applied to individual stroke subjects based on census tract of residence and year of stroke presentation. Average neighborhood disadvantage score was used when there were overlapping years of the American Community Survey data.

Air Pollution and Meteorology Data

Hourly PM_{2.5}, O₃, and meteorological data for 2000 to 2012 were obtained from the Texas Commission on Environmental Quality's Texas Air Monitoring Information System²² for a centrally located monitor within the urban population. PM_{2.5} was measured using a tapered element oscillating microbalance and O₃ was measured using an ultraviolet absorption analyzer. Relative humidity was calculated using dew point temperature from the Corpus Christi International airport with data from the National Oceanic and Atmospheric Administration.^{23,119} PM_{2.5}, ambient temperature, and relative humidity were averaged daily and the maximal 8-hour daily average was calculated for O₃. These summary measures were calculated for each day of the study period and are based on the US Environmental Protection Agency National Ambient Air Quality Standards for daily PM_{2.5} and daily maximum 8-hour concentration for O₃.¹²²

Statistical Methods

Characteristics of the study population were summarized with descriptive statistics both overall and by neighborhood disadvantage score, comparing the 90th percentile to the 10th percentile. Continuous variables were compared using t-tests or non-parametric Wilcoxon tests, when appropriate. Categorical variables were compared using chi-square tests. The distribution

of NIHSS was examined visually using density plots by neighborhood disadvantage level and air pollution level.

The association between neighborhood disadvantage, air pollutants ($PM_{2.5}$ and O_3), and initial NIHSS was modeled in two ways based on previous work.¹⁷ We used linear models for continuous NIHSS score and logistic regression models comparing the upper quartile of severity (severe stroke, $NIHSS \geq 7$) to all lower quartiles (mild stroke, $NIHSS < 7$). Generalized estimating equations were used to account for clustering of stroke subjects within census tracts. Modeling was done in three stages. First, the main effects of neighborhood disadvantage and each air pollutant (same-day $PM_{2.5}$ and previous-day O_3 based on previous work in this population¹⁵¹) on NIHSS score were examined separately in single exposure models, adjusting for demographics (race/ethnicity, age and gender) and stroke risk factors (atrial fibrillation, coronary artery disease, diabetes, hypertension, and smoking status). The air pollution models were additionally adjusted for ambient temperature, humidity, day of the week, and season. Second, the main effects of neighborhood disadvantage and each air pollutant were examined together in dual exposure models. Third, the interaction between each air pollutant and neighborhood disadvantage was added to the dual exposure models. Additionally, co-pollutant models with both air pollutants included were examined to explore the potential confounding effects. We assessed the functional forms of the neighborhood disadvantage, air pollutants and meteorological variables using quartiles and penalized polynomial splines. Although the distribution of NIHSS score was right skewed, its relation with air pollution was approximately linear and thus we maintained the original variable for ease of interpretation. We additionally found linear functional forms to be appropriate for neighborhood disadvantage, and both meteorological variables. Associations between neighborhood disadvantage and NIHSS score

were summarized as a comparison of the 90th to the 10th percentile of the neighborhood disadvantage score. Differences in NIHSS score were calculated for 10 µg/m³ or 10 ppb change in PM_{2.5} and O₃, respectively. In the presence of effect modification of the air pollution-stroke severity association by neighborhood disadvantage, indicated by a statistical interaction term p-value < 0.10, estimates of the air pollution-stroke severity association at the 10th and 90th percentiles of neighborhood disadvantage score were reported.

Sensitivity Analysis

Quantile regression was conducted at the 75th percentile of NIHSS score to bridge the understanding between the results of the linear and logistic models. Quantile regression models the conditional percentile of the NIHSS score as a linear function of individual characteristics allowing for the ability to estimate quantile-specific effects at any point within the distribution,^{152,153} providing a continuous severity score interpretation among those that had a severe stroke.

All analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC). The BASIC project was approved by the University of Michigan Institutional Review Board and each of the Nueces County hospital systems.

4.3 Results

There were 3,035 individuals with ischemic strokes included in this analysis after excluding 92 individuals that were unable to be geocoded and 276 strokes that occurred on days with missing air pollutant exposure information. The median age was 70 years with an interquartile range (IQR) of (59-80 years) (Table 4-1). Fifty-one percent of the stroke cases were women, 53% were Mexican American, 42% were non-Hispanic White and 5% were African American. The median initial stroke severity was 4 (IQR: 2-7). Those residing in a census tract

with high neighborhood disadvantage (90th percentile) were younger, less likely to be non-Hispanic White, and were more likely to have a history of diabetes compared to those living in a census tract with low neighborhood disadvantage (10th percentile, Table 4-1).

Neighborhood Disadvantage

Neighborhood disadvantage was not associated with continuous NIHSS score or the odds of severe stroke in the single exposure models (Table 4-2). Neighborhood disadvantage was also not associated with continuous NIHSS score in models the dual exposure models adjusting for same-day PM_{2.5} or previous-day O₃. In the logistic models comparing the odds of severe to mild stroke adjusting for same-day PM_{2.5}, the association between neighborhood disadvantage was borderline significant (OR comparing the 90th to the 10th percentile of neighborhood disadvantage: 1.24, 95% CI: 0.98-1.57). The neighborhood disadvantage-severe stroke association was of similar magnitude (OR: 1.22, 95% CI: 0.96-1.53) after adjusting for previous-day O₃, but failed to reach statistical significance.

Air Pollutants

Same-day PM_{2.5} was not associated with continuous NIHSS score or the odds of severe stroke, in either the single exposure models or the dual exposure models (Table 4-2). However, previous-day O₃ was associated with both continuous NIHSS score and the odds of severe stroke in both single and dual exposure models. In the single exposure models, a 10 ppb higher previous-day O₃ level was associated with higher NIHSS score (mean difference: 0.22, 95% CI: 0.04-0.41) and an increased odds of severe stroke (OR: 1.10, 95% CI: 1.02-1.17). The associations were of similar magnitude in the dual exposure models.

Effect Modification by Neighborhood Disadvantage

Neighborhood disadvantage modified the association between PM_{2.5} and odds of severe stroke (p=0.03), but not the association between PM_{2.5} and continuous NIHSS score. Among those living in areas of higher neighborhood disadvantage (90th percentile of neighborhood disadvantage score), a 10 µg/m³ higher same-day PM_{2.5} level was associated with a 30% higher odds of severe stroke for (95% CI: 1.03-1.64), whereas the association was not observed among those in areas of lower neighborhood disadvantage (10th percentile of neighborhood disadvantage score OR: 0.78, 95% CI: 0.56-1.08). The associations between O₃ and continuous NIHSS score and severe stroke were not modified by neighborhood disadvantage.

The results of the models were consistent when mutually adjusted for both pollutants (results not shown).

Sensitivity Analyses

The quantile regression models at the 75th percentile of the NIHSS score distribution were consistent with the results observed in the logistic models. Neighborhood disadvantage was not associated with NIHSS score at the 75th percentile in the single exposure model, but was borderline associated with higher NIHSS score after adjustment for same-day PM_{2.5} in the dual exposure model (Table 4-3). For previous-day O₃, a 10 ppb higher O₃ level was associated with a 0.26 point higher NIHSS score at the 75th percentile in both single (95% CI: 0.04-0.47) and dual exposure models (95% CI: 0.05-0.46). The association between same-day PM_{2.5} and NIHSS score was larger among those living in an area of higher neighborhood disadvantage compared to lower neighborhood disadvantage (p=0.004), but the association between O₃ and NIHSS score was not modified by neighborhood disadvantage.

4.4 Discussion

This population-based stroke study suggests that environmental factors are associated with stroke severity and that neighborhood disadvantage and air pollution may have unique contributions. Living in an area of high neighborhood disadvantage increased the likelihood of a severe ischemic stroke compared to living in an area of low neighborhood disadvantage. There was an association between PM_{2.5} and severe stroke that was only evident in areas of high neighborhood disadvantage. However, higher O₃ levels were associated with severity and this association did not vary by neighborhood disadvantage. We observed these associations between the environment and severity after accounting for known individual predictors for severity, suggesting that environmental features explain additional variation in stroke severity. Specifically, with findings for both air pollution and neighborhood disadvantage, our results suggest that multiple dimensions of the neighborhood environment may be meaningful for understanding stroke severity.

Understanding how neighborhood disadvantage may influence stroke severity is important, as severity is an important predictor of stroke outcomes³⁻⁷ and thus an understanding of risk factors for severe stroke could suggest novel intervention targets to improve outcomes. Neighborhood socioeconomic conditions may influence risk factors for severe stroke. The availability of healthy food, safe areas for walking or other forms of exercise and access to health care are some examples of environmental features that contribute to hypertension, smoking, and obesity.⁸⁹⁻⁹² Risk factors for severe stroke, such as atrial fibrillation, physical inactivity, obesity, and smoking, and lower adherence to medications have been found to be more prevalent among those residing in poorer neighborhoods compared to those in richer neighborhoods and thus may contribute to more severe strokes.^{88,154,155} Neighborhood may also serve as a proxy for

neighborhood stressors, such as neighborhood violence and disorder, which may influence physiologic stress response.^{93,94} Physiologic stress responses due to neighborhood conditions have also been linked to increased risk of ischemic disease¹⁵⁶ and fatal ischemic stroke,¹⁵⁷ suggesting a possible pathway involving stroke severity. The lack of safe environments available to residents may impact their ability to exercise and may influence their ability to live a healthy lifestyle. Neighborhood disadvantage may also impact other factors important to stroke severity, such as stroke awareness and hospital delay times^{95,96} and air pollution.

Our study is the first to report an association between O₃ and stroke severity. Higher levels of O₃ were associated with higher stroke severity and greater odds of severe stroke. The exact mechanism linking O₃ to stroke severity is unclear. O₃ could influence stroke severity through vasoconstriction, as higher blood pressure may reflect higher stroke severity.¹⁵⁸ O₃ is also a strong oxidant and may affect severity via inflammation as C-reactive protein⁵⁴ and homocysteine⁵⁵ are associated with higher severity at admission. Another hypothesis is that O₃ may act as an acute trigger for a cardioembolic stroke among those with atrial fibrillation, since O₃ has been linked to heart rate variability^{159,160} and atrial fibrillation^{161,162} and atrial fibrillation is a predictor of severe stroke.¹³⁹ This pathway, however, is not supported by previous work that reported no association between air pollutants (nitrogen oxides, carbon monoxide, and ultrafine particles) and atrial fibrillation related ischemic strokes or severe ischemic strokes.¹⁶ However, O₃ was not explored. Future work should try to replicate our results with O₃ and consider possible pathways by which O₃ influences severe stroke.

There are plausible explanations for the observed synergism between neighborhood disadvantage and PM_{2.5} on stroke severity. Neighborhood disadvantage could influence the impact of air pollution on severity if there is greater susceptibility among those in more

disadvantaged neighborhoods. Those in areas of greater neighborhood disadvantage experience more psychosocial stress and violence, which has been shown to increase susceptibility to air pollution for asthma via oxidative stress and inflammation,^{101,102} and may do so similarly for stroke as oxidative stress¹⁰³ and C-reactive protein influence severity.¹⁰⁴ Greater susceptibility to air pollution could also be due to nutritional deficits from lack of healthy food availability. Studies have shown that antioxidant vitamins and n-3 polyunsaturated fatty acids might protect against acute the adverse influences of air pollution,^{105–108} such that individuals with diets lacking in these nutrients may have increased susceptibility to the effects of air pollution. Additionally, areas with worse housing conditions may have differential air pollution infiltration. Housing without air conditioning may promote more open windows, and thus higher infiltration of air pollution.¹⁶³ Housing stock may also help to explain why effect modification by neighborhood disadvantage was only present for PM_{2.5}. O₃, as a secondary pollutant, does not penetrate the indoor environment very well,¹⁴¹ whereas PM_{2.5} does but is linked with housing characteristics.¹⁶³ Although this hypothesis is plausible, further research to explore synergistic effects between neighborhood characteristics and air pollution on stroke severity and how this may vary for different air pollutants is needed.

There are some limitations of our study that warrant discussion. The clinical significance of the observed differences in NIHSS score is unclear; however larger fluctuations in pollution levels would have stronger associations with severity. There was only one air pollution monitor in the county that had daily air pollution data during the course of our study. Therefore, individual air pollution exposure may be misclassified, and could introduce measurement error in our models if the daily fluctuations were not homogeneous across the county. However, PM_{2.5} measured every three to six day at another monitor in the county showed large correlations

($p \geq 80\%$) with the single monitor used in our study. Future studies with greater spatial resolution of air pollution data would be able to answer questions of the long-term associations with stroke severity. We were unable to control for individual-level SES in our analysis as it was not available on the full data set, and while neighborhood and individual SES effects can be independent of one another,^{164–166} individual SES may explain some of the differences we observed. Competing risks of other cardiovascular outcomes may have played a role in our ability to observe associations between air pollution and stroke severity; air pollution exposures could have triggered other outcomes linked to these exposures such as myocardial infarction, intracerebral hemorrhage, or death such that competing risks may remove those that would have had the most severe strokes from the at-risk population and reduce the observed association between air pollution and stroke severity.

We observed that living in an area of higher neighborhood disadvantage was associated with an increased likelihood of having a severe ischemic stroke relative to living in an area of lower disadvantage. Higher levels of O_3 influenced both stroke severity and the odds of having a severe stroke, while the influence of $PM_{2.5}$ on the odds of having a severe stroke was only evident in more disadvantaged neighborhoods. This was the first study to specifically look at the synergistic association between air pollution and neighborhood disadvantage on stroke severity. Our results suggest that the environment may be important in understanding stroke severity and future work should consider the multiple levels of influence on this important outcome.

Table 4-1 Characteristics (N, %) of 3035 Incident Ischemic Strokes in Nueces County, Texas, 2000-2012 Overall and by High/Low Neighborhood Disadvantage (90th vs. 10th percentiles).

Characteristic	Overall (N=3035)	Low ND (N=320)	High ND (N=313)	<i>P</i>
Age, median (Q1, Q3), yrs	70 (59, 80)	73 (62, 82)	69 (58, 78)	<0.001
Female	1558 (51.3)	164 (51.3)	157 (50.2)	0.784
Race/Ethnicity				<0.001
Non-Hispanic White	1258 (41.5)	240 (75.0)	20 (6.4)	
Mexican American	1609 (53.0)	73 (22.8)	268 (85.6)	
African American	168 (5.5)	7 (2.2)	25 (8.0)	
NIHSS, median (Q1, Q3)	4 (2, 7)	4 (2, 7)	4 (2, 7)	0.521
Medical History				
Atrial fibrillation	398 (13.1)	46 (14.4)	36 (11.5)	0.282
Coronary artery disease	924 (30.4)	104 (32.5)	96 (30.7)	0.64
Diabetes mellitus	1235 (40.7)	88 (27.5)	161 (51.4)	<0.001
High cholesterol	975 (32.1)	103 (32.2)	83 (26.5)	0.117
Hypertension	2292 (75.5)	233 (72.8)	235 (75.1)	0.516
Excessive alcohol use	198 (6.5)	16 (5.0)	25 (8.0)	0.127
Smoking History				
Current	637 (21.0)	62 (19.4)	75 (24.0)	0.161
Former	374 (12.3)	52 (16.3)	36 (11.5)	0.084

ND: Neighborhood disadvantage; Q: Quartile; NIHSS: National Institutes of Health Stroke Scale.

Table 4-2 Results of linear and logistic models of initial stroke severity (NIHSS score) with environmental exposures.

	Continuous NIHSS*		Dichotomous NIHSS ≥ 7 *	
	Mean Diff. (95% CI)	p-value	OR (95% CI)	p-value
Single Exposure Models^{††}				
Neighborhood disadvantage [§]	0.21 (-0.38, 0.80)	0.489	1.22 (0.96, 1.55)	0.104
Same-day PM _{2.5} ^{‡‡}	-0.11 (-0.57, 0.36)	0.656	1.01 (0.85, 1.19)	0.939
Previous-day O ₃ ^{‡‡}	0.22 (0.04, 0.41)	0.019	1.10 (1.02, 1.17)	0.009
Same-day PM_{2.5}				
Dual Exposure Models ^{††}				
Neighborhood disadvantage [§]	0.26 (-0.31, 0.83)	0.377	1.24 (0.98, 1.57)	0.069
PM _{2.5} ^{‡‡}	-0.10 (-0.56, 0.36)	0.665	1.01 (0.86, 1.19)	0.900
Exposure Interaction Models ^{‡‡§#}				
PM _{2.5} - Low neighborhood disadvantage	-	-	0.78 (0.56, 1.08)	0.138
PM _{2.5} - High neighborhood disadvantage	-	-	1.30 (1.03, 1.64)	0.028
PM _{2.5} - Neighborhood disadvantage interaction		0.392		0.033
Previous-day O₃ (Max 8hr)				
Dual Exposure Models ^{††}				
Neighborhood disadvantage [§]	0.21 (-0.37, 0.78)	0.480	1.22 (0.96, 1.53)	0.102
O ₃ ^{‡‡}	0.22 (0.03, 0.40)	0.020	1.09 (1.02, 1.17)	0.010
Exposure Interaction Models ^{‡‡§#}				
O ₃ - Neighborhood disadvantage interaction		0.889		0.157

NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio; CI: Confidence Interval; PM_{2.5}: Particulate matter less than 2.5 um in diameter; O₃: Ozone

* All models adjusted for age, sex, Mexican American ethnicity, African American race, history of atrial fibrillation, coronary artery disease, diabetes, hypertension, and smoking status

† Models with pollutants additionally include temperature, relative humidity, day of the week, and season

‡ All effects are for a 10 µg/m³ or 10 ppb increase in PM_{2.5} or O₃ exposure, respectively

§ Higher neighborhood disadvantage score represents more neighborhood disadvantage, comparing the 90th to the 10th percentile of neighborhood disadvantage score

†† Single exposure models include just one of the two environmental exposures, air pollutant or neighborhood disadvantage score. Dual exposure models include both air pollutant and neighborhood disadvantage score

Exposure interaction models include both air pollutant and neighborhood disadvantage score as well as their interaction

Table 4-3 Sensitivity analysis. Continuous NIHSS score at the 75th percentile using quantile regression with environmental exposures.

	Continuous NIHSS* at the 75th percentile	
	Mean Diff. (95% CI)	p-value
Single Exposure Models^{††}		
Neighborhood disadvantage score [§]	0.54 (-0.45, 1.53)	0.283
Same-day PM _{2.5} ^{‡‡}	0.12 (-0.46, 0.71)	0.676
Previous-day O ₃ ^{‡‡}	0.26 (0.04, 0.47)	0.018
Same-day PM_{2.5}		
Dual Exposure Models ^{††}		
Neighborhood disadvantage score [§]	0.73 (-0.12, 1.59)	0.093
PM _{2.5} [‡]	0.17 (-0.44, 0.77)	0.589
Exposure Interaction Models ^{†‡§#}		
PM _{2.5} – Low neighborhood disadvantage score	-0.64 (-1.33, 0.04)	0.066
PM _{2.5} – High neighborhood disadvantage score	1.19 (0.37, 2.00)	0.004
PM _{2.5} – Neighborhood disadvantage score interaction		0.004
Previous-day O₃ (Max 8hr)		
Dual Exposure Models ^{††}		
Neighborhood disadvantage score [§]	0.66 (-0.25, 1.57)	0.156
O ₃ [‡]	0.26 (0.05, 0.46)	0.013
Exposure Interaction Models ^{†‡§#}		
O ₃ – Neighborhood disadvantage score interaction		0.423

NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio; CI: Confidence Interval; PM_{2.5}: Particulate matter less than 2.5 um in diameter; O₃: Ozone

*All models adjusted for age, sex, Mexican American ethnicity, African American race, history of atrial fibrillation, coronary artery disease, diabetes, hypertension, and smoking status

[†]Models with pollutants additionally include temperature, relative humidity, day of the week, and season

[‡]All effects are for a 10 µg/m³ or 10 ppb increase in PM_{2.5} or O₃ exposure, respectively

[§]Higher neighborhood disadvantage score represents more neighborhood disadvantage, comparing the 90th to the 10th percentile of neighborhood disadvantage score

^{††}Single exposure models include just one of the two environmental exposures, air pollutant or neighborhood disadvantage score. Dual exposure models include both air pollutant and neighborhood disadvantage score

[#]Exposure interaction models include both air pollutant and neighborhood disadvantage score as well as their interaction

Chapter 5

Discussion

5.1 Overall Summary of Research and Finding

This dissertation investigated associations between aspects of the environment, including air pollution and neighborhood disadvantage, and stroke risk and severity in Nueces County, Texas between 2000 and 2012. Ethnicity, sociodemographic and clinical factors, and neighborhood disadvantage were additionally explored as subgroups/factors that may influence susceptibility to the effects of the environment on stroke. Identification of these associations could inform policy and interventions targeted at improving stroke risk and outcomes, as well as efforts aimed at environmental justice.

Chapter 2 investigated overall associations between two air pollutants, PM_{2.5} and O₃, and ischemic stroke risk, and whether these associations were modified by ethnicity. Using validated stroke data from the BASIC project, we observed overall suggestive associations between O₃ and risk of incident ischemic stroke, but no overall associations for PM_{2.5}. These suggestive associations for O₃ were strongest at lags of 1 and 2 days prior to stroke. The PM_{2.5}-incident stroke association was only present among MAs and was not observed among NHWs and conversely, the O₃-incident stroke association was only present among NHWs and was not observed among MAs. Similar associations were not observed for recurrent stroke. In Chapter 3, no associations were found between the air pollutants and ischemic stroke recurrence. In the same chapter, we further investigated effect modification of the air pollution-stroke recurrence association by sociodemographic and clinical factors, but largely had null findings. Chapter 4

focused on air pollution and neighborhood disadvantage as aspects of the environment that may influence initial stroke severity. We found that living in areas of greater neighborhood disadvantage was associated with an increased likelihood of a severe ischemic stroke compared to living in areas of lesser disadvantage after accounting for individual-level age, sex, race/ethnicity, smoking status, and comorbid conditions. Further, higher levels of PM_{2.5} were associated with the odds of severe stroke, but only among more disadvantaged neighborhoods, while higher levels of O₃ were associated with stroke severity similarly across neighborhoods. The culmination of this dissertation suggests that air pollution (particularly O₃) may influence stroke risk and severity and that future work should be conducted in diverse populations to better understand ethnic differences in susceptibility to the harmful effects of air pollution. The research also suggests that factors beyond individual risk factors may influence stroke severity and may provide a novel means to intervene to improve this outcome.

5.2 Aims 1 and 2

Summary

Chapters 2 and 3 investigated the associations between PM_{2.5} and O₃ and incident ischemic stroke and recurrent ischemic stroke, respectively. Further, Chapters 2 and 3 explored whether the air pollution-stroke associations are modified by ethnicity (Chapter 2) and whether certain subgroups are more vulnerable to the impact of air pollution on recurrence (Chapter 3). Air pollution levels were low in our study, with median levels of 7.7 µg/m³ for PM_{2.5} and 35.7 ppb for O₃, which are below the US EPA NAAQS thresholds of 35.0 µg/m³ for daily PM_{2.5} and 75 ppb for fourth highest daily maximum 8-hour concentration for O₃.¹²² However, we still observed a suggestive association between O₃ and incident ischemic stroke, but no associations were observed between either air pollutant and stroke recurrence. O₃ levels were borderline

significantly associated with the odds of incident ischemic stroke with the strongest associations for lags 1 and 2. A 10 ppb higher lag 1 (or 2) O₃ was associated with a 2% increase in the odds of stroke (95% CI: 0.99-1.06). And while we observed these suggestive associations, increased risk of ischemic stroke from O₃ was only observed among NHWs, with one interaction between O₃ and ethnicity reaching borderline significance. For a 10 ppb higher lag 2 O₃ concentration, NHWs experienced a 6% higher odds of ischemic stroke (95% CI: 1.00-1.11) while no association was observed in MAs (OR: 1.00, 95% CI: 0.92-1.05). In contrast, for a 10 µg/m³ higher same-day PM_{2.5} concentration, we observed a 12% greater odds of an ischemic stroke in MAs (95% CI: 0.98-1.27), but a 7% lower odds of an ischemic stroke in NHWs (95% CI: 0.80-1.08). The reasons for these contrasting findings between PM_{2.5} and O₃ by ethnicity are not clear. Possible explanations may be ethnic differences in biologic susceptibility or differential exposure levels to the two pollutants by ethnicity. Both of these explanations could not be tested in our study and suggest that additional research is needed in diverse populations to investigate ethnic-specific effects.

Advances to the Field

Our work advances the field of air pollution-stroke research by utilizing a case-crossover design with 13 years of validated stroke data in an ethnically diverse community. This was only the third case-crossover study in the US to look at the air pollution-stroke association and the third study to specifically look at the air pollution-recurrence association. The use of a time-stratified case-crossover design in Aims 1 and 2 allowed for tight control of individual level confounders (both known and unknown) and slow-varying seasonal effects.^{114,115,167} One of the biggest strengths of this design is the assessment of the “Why now?” question instead of “Why me?” as is done in time-series analyses. This design focuses solely on what has changed over a

short interval preceding the outcome, and lends itself to considering differential effects via effect modification very easily. Further, much of the previous work using the case-crossover design has included both incident as well as recurrent strokes when assessing the association with air pollution.^{10,14,70} The inclusion of both types of strokes in a composite endpoint precludes an understanding of how air pollution may impact incident and recurrent stroke differently. We allowed for careful consideration of how air pollution may uniquely influence these two stroke endpoints with strict definitions of first-ever stroke in Aim 1 and first recurrent stroke in Aim 2. Specifically, for Aim 2 we identified incident ischemic strokes with no reported history of prior stroke or TIA and then captured their first subsequent ischemic stroke. And, as such, we were able to quantify the amount of time between incident and recurrent stroke. This is important because we know that the background risk for stroke recurrence changes over time,^{26,73} and we observed the suggestion of differential effects by time since previous stroke. Stronger effects were suggested between PM_{2.5} and recurrence within 90 days of the first stroke event and yet were inexplicably protective within one year for the effect between O₃ and recurrence.

The BASIC data additionally provided good measurement of factors that may identify vulnerable subgroups. For example, we were able to consider effect modification by race/ethnicity,¹¹⁶ a host of comorbid conditions, and other sociodemographic factors. Our study was the first to examine effect modification of the air pollution-incident stroke association by ethnicity, as well as the first to look at a comprehensive list of potential effect modifiers of the air pollution-recurrence association. We also thoroughly investigated the functional forms of both pollutants and confounders across all models to ensure that we correctly modeled the relation between the exposures, their variables, and the outcomes. In an effort to examine the robustness of our associations and to further explain them, we also performed sensitivity

analyses. Across both Aims 1 and 2, we evaluated co-pollutant models to examine the potential confounding effects that PM_{2.5} and O₃ may have on their respective associations with incident and recurrent stroke. We also repeated the analyses in Aims 1 and 2 among those individuals residing closer to the air pollution monitor as an evaluation of the degree of air pollution exposure misclassification in the analyses. Aim 1 models were additionally repeated including interaction terms between indicators of downwind day and history of diabetes and the air pollutants to explore possible causes of the modification of the air pollution-stroke association by ethnicity. By observing suggestive associations between O₃ and incident stroke and effect modification by ethnicity, our results suggest that further study in diverse populations is warranted and more research is necessary to understand the influence of air pollution and stroke recurrence.

Comparisons to Prior Work

The results of our study are comparable to associations observed between air pollution and ischemic stroke risk in some previous studies, although previous studies have not been entirely consistent. Two case-crossover studies from Canada reported no association between ischemic stroke risk and PM_{2.5} with similar PM_{2.5} pollution levels to our study.^{13,62} However, a study in Boston, MA found that higher PM_{2.5} concentrations in the 24 hours preceding stroke were associated with an increased odds of ischemic stroke.¹⁴ For O₃, case-crossover studies in Massachusetts,¹⁴ Pennsylvania,⁷⁰ and France¹⁰ observed no association with ischemic stroke, while a second French study reported an association with stroke.¹¹ Previous work in this study community by Lisabeth et al. utilizing a time-series approach found suggestive associations between both same-day and previous-day PM_{2.5} and O₃ and risk of ischemic stroke/TIA.⁶⁵ Our results were similar to this previous study for O₃, but not for PM_{2.5}. These differences may be

due to differences in study design (time-series vs. case-crossover) and classification of the stroke endpoints as the previous study included both incident and recurrent ischemic strokes and TIAs in the outcome, whereas our analysis was limited to incident ischemic strokes only.

Very few studies have investigated the relation between air pollutants and recurrent stroke, however, previous case-crossover studies have reported associations between higher levels of ambient air pollution and risk of recurrent stroke.^{10,14,72,130} One study explored those with a history of stroke as a secondary subgroup analysis,¹⁴ while two studies in France explicitly designed their studies around recurrent stroke as an outcome.^{10,72} Another study examined history of stroke as a further exploration of their air pollution-stroke association, but the information on the methodology was limited as it was not a peer reviewed analysis.¹³⁰ Recurrent ischemic strokes are challenging to investigate. Approximately one-quarter of the yearly strokes in the US are recurrent,²⁵ limiting the number of available recurrent strokes for study. The rationale behind our study design (limiting to first recurrent stroke following incident event) was to remove some of the ambiguity in the definitions of recurrent strokes from prior studies. Not knowing the previous stroke history for each individual may violate the constant background risk assumption of the case-crossover model design. If the risk for stroke recurrence changes after each subsequent stroke, we may not be isolating to true association between air pollution and recurrent stroke. Unfortunately, in our restriction, we may have decreased our ability to identify an association by limiting our sample so rigorously.

Implications

The suggestion of ethnic differences in the association between air pollution and stroke is important in terms of environmental justice. It is unclear whether these differences are due to biologic susceptibility, ethnicity being a proxy of other socioeconomic markers of deprivation,

differences in exposure, or chance, and thus further study is warranted to investigate these different possibilities. Biologic susceptibility would be the most challenging hypothesis to test, perhaps needing genetic study or additional laboratory studies to understand air pollution associations on a microbiologic level. If ethnicity only acts as a proxy for a measure of socioeconomic status, co-adjustment of both effect modifiers (ethnicity and socioeconomic status by air pollution) in statistical models should fully explain ethnic differences. If the ethnic differences are due to differences in exposure, as a result of housing availability, greater industrial presence, or proximity to roadways, environmental exposure regulations (NAAQS attainment for criteria pollutants) could be evaluated to provide safer air conditions for those living in more polluted areas. If minorities or other vulnerable groups are more susceptible to the influences of air pollution, additional studies in diverse populations are critical in order to identify the groups with the greatest need for protection. The US EPA is required to protect the most susceptible, yet much of the science that is used to set the standards is based on non-Hispanic whites. If minorities have stronger associations with air pollution, then the EPA's obligations to adequately protect these vulnerable subgroups may not be being fulfilled and this would provide evidence for stricter standards.

The results of Aim 2 were inconsistent with previous findings and suggest that more work is needed to understand the relation between air pollution and stroke recurrence. A key piece to understanding the association may be in the amount of time since first stroke. Stronger effects were suggested between PM_{2.5} and recurrence within 90 days of the first stroke event and yet inexplicably protective within one year for the effect between O₃ and recurrence. Timing of stroke recurrence is a complicated issue. As more time passes, the likelihood of a competing event (i.e. hemorrhagic stroke, death, etc.) increases, which would prevent inclusion in our

recurrent stroke endpoint and likely results in some level of survivor bias in the sample. One way to adjust for survivor bias in these studies could be upweighting recurrent stroke cases that were similar in terms of demographic and other characteristics as those who died or had a hemorrhagic stroke prior to a recurrent ischemic stroke. The weighted analyses could then be compared to the original analyses to understand the extent that selection issues are influencing the null results. Strokes that occur close in time to the previous stroke may be an additional issue, as it may be hard to differentiate recurrent stroke from the incident event. If the associations between incident and recurrent strokes and air pollution are different, including a recurrent stroke that is very close in time to an incident stroke may actually capture the air pollution-incident stroke association, rather than getting a true estimate of the air pollution-stroke recurrence association. While we only observed 86 strokes that occurred within 90 days, our findings in combination with what is known about risk of recurrent stroke over time suggests larger studies are needed and that time since the first stroke should be carefully considered in future studies of recurrent stroke. If there is a greater risk of having a recurrent stroke due to the influence of air pollution shortly after a first stroke, it becomes important to educate stroke patients of the dangers and risks associated with air pollution exposure during this vulnerable period.

5.3 Aim 3

Summary

Chapter 4 identified that both air pollution and neighborhood disadvantage influence initial stroke severity. Residing in more disadvantaged neighborhoods was suggestively associated with higher odds of severe stroke relative to residing in less disadvantaged neighborhoods. Further, higher concentrations of O₃ were associated with more severe stroke and higher odds of severe stroke. Similarly, higher concentrations of PM_{2.5} were associated with

higher odds of severe stroke, but only among those that live in more disadvantaged neighborhoods.

Advances to the Field

This work specifically adds to the literature as only one other US study has explored the association between neighborhood disadvantage and stroke severity,¹⁷ and only two studies have focused on the association between air pollution and stroke severity.^{15,16} We took this a step further by being the first study to look at whether aspects of the environment work synergistically to influence stroke severity. In addition to using a single measure of disadvantage, the previous US study used census data from one point in time to measure disadvantage.¹⁷ We, however, created a time-dependent composite neighborhood disadvantage score using 12 different factors across multiple dimensions of disadvantage using census data from three different time periods. By using census data collected closer to the time of stroke we reduced misclassification of disadvantage level at the time of stroke occurrence. We also examined the functional form of the environmental exposures to assess whether the associations between the exposures and stroke severity behaved linearly and comprehensively adjusted for individual-level confounders in all models to reduce possible bias. In addition, as a sensitivity analysis, we used quantile regression to demonstrate the bridge between the continuous and dichotomous severity models to show the robustness of our results. By finding associations with both air pollution and neighborhood disadvantage and stroke severity, our results suggest that the environment may have a multi-dimensional influence on severity and consideration of multiple levels of risk factors beyond individual-level factors should be investigated in future studies.

Comparisons to Prior Work

Limited prior studies have examined the relation between neighborhood disadvantage and stroke severity in the US¹⁷ and in Scotland⁸⁹ and two European studies have examined the relation between air pollution and severity.^{15,16} Similar to Kleindorfer et al.¹⁷ and Aslanyan et al.,⁸⁹ we observed that higher levels of neighborhood disadvantage were associated with higher initial stroke severity. However, in contrast to Maheswaran et al.¹⁵ and Andersen et al.,¹⁶ we found that higher concentrations of air pollution were associated with greater odds of severe stroke, while the prior studies reported stronger associations between air pollution and mild, but not severe stroke. It is unclear why our air pollution-severe stroke associations would differ from these previous studies. Maheswaran et al. hypothesized that the thrombus formation due to air pollution may be less dense and more modest in size or more easily broken down, however, our findings do not support this hypothesis. It is possible that the distribution of effect modifiers (ethnicity, SES, etc.) of the air pollution-severe stroke association was different between the two studies accounting for the differences in observed associations. Additional work is needed to further understand the association between air pollution and stroke severity.

While higher levels of O₃ were uniformly associated with more severe stroke across neighborhoods, higher levels of PM_{2.5} were associated with severe stroke but only in more disadvantaged neighborhoods. It is unclear why the PM_{2.5} association with severe stroke would be modified by neighborhood disadvantage, but not the O₃ association. Spatial variability is one hypothesis, but with only one monitor for both pollutants in the study, we could not investigate whether O₃ concentrations were more uniform across the county and PM_{2.5} concentrations were higher in more disadvantaged areas. Aside from possible differences in exposure across the pollutants in the study, there are plausible explanations for the observed synergism between

neighborhood disadvantage and air pollution. Neighborhoods with more disadvantage may have more individuals with increased susceptibility to the negative health effects of air pollution. Work in asthma has shown greater susceptibility to air pollution in areas of greater neighborhood disadvantage through more psychosocial stress and violence.^{101,102} This may work similarly in stroke since oxidative stress¹⁰³ and C-reactive protein, as markers of inflammation, influence severity.¹⁰⁴ Other pathways to differential susceptibility to air pollution include nutritional deficits due to healthy food availability, since antioxidant vitamins and n-3 polyunsaturated fatty acids might protect against the adverse influences of air pollution.^{105–108} Housing stock may also contribute to why only the PM_{2.5}-severity association was modified by neighborhood disadvantage. Availability of air conditioning in housing can influence infiltration of air pollutants indoors;¹⁶³ O₃ does not penetrate the indoor environment as well as PM_{2.5},¹⁴¹ which is more linked with housing characteristics.¹⁶³ Additional work is necessary to further study possible mechanisms behind the synergistic association of environmental features on stroke severity.

Implications

The identification of multiple features of the environment that influence stroke severity beyond individual-level factors is important for several reasons. Interventions can target features of the environment that can benefit populations of people and get “more bang for their buck”. Initial stroke severity is one of the most important predictors of stroke outcomes,^{3–7} so knowing factors that influence severity could improve stroke outcomes. By working with disadvantaged communities to educate them on stroke symptoms and transportation methods, delay times could be reduced which may improve initial severity and increase stroke treatment. Improved monitoring of pollutants across all areas may also be an area of future interest to enhance the

ability to assess differential air pollutant exposures. Evidence of differential exposure across neighborhoods linked to health consequences, such as stroke and stroke severity, may encourage change toward environmental justice in this and other communities.

5.4 Strengths and Limitations

As previously described in the above sections, this dissertation work has numerous strengths. Overall, this dissertation used 13 years of population-based stroke surveillance data to investigate the associations between air pollution and stroke risk, recurrence and severity, investigate previously unexplored ethnic differences in air pollution-stroke associations, investigate sociodemographic and clinical differences in air pollution-recurrent stroke associations, investigate the association between neighborhood disadvantage and initial stroke severity, and investigate the potential synergism between neighborhood features on initial stroke severity. The strengths of this work span across the three Aims and hit multiple dimensions such as study design, study population, measurement, and sensitivity analyses. The use of time-stratified case-crossover designs in Aims 1 and 2 allowed for tight control of individual level confounders and seasonal effects.^{114,115,167} The study population was a specific strength of Aim 1. The BASIC study population is uniquely suited for the study of ethnic differences in the air pollution-stroke association (Aim 1), as no other study has the necessary volume of validated strokes among Hispanic Americans to adequately examine this issue. This dissertation further benefited from the use of the BASIC project data in methodological aspects by allowing the consideration of three different stroke endpoints (incident and recurrent strokes and initial stroke severity) and having good measurement of factors that may identify vulnerable subgroups. Aim 3 additionally improved on the previous measurement of neighborhood disadvantage with the creation of a time-dependent composite score using 12 different factors across multiple

dimensions of disadvantage. We additionally conducted multiple sensitivity analyses for each Aim in an effort to examine the robustness of our associations and to further explain our observations.

There are limitations to each Aim of this dissertation. The largest limitation is that there was only one air pollution monitor that continuously collected PM_{2.5} and O₃ concentrations for the duration of the study period. Assigning air pollution exposures to each stroke case across the county likely resulted in some level of exposure misclassification, as it is unlikely that the concentrations were homogenous across space. However, daily concentrations were highly correlated with another fixed monitor in the county for PM_{2.5}, for concentrations measured every third or sixth day ($\rho > 0.80$) and the relatively flat topography of Nueces County,¹²⁵ suggests that the exposures are likely to be correlated across space. We also assume that the ambient air pollution concentrations are surrogates for personal and indoor pollutant exposures. Prior work has suggested that indoor and outdoor concentrations of PM_{2.5} are correlated, but that may not be the case for concentrations of O₃.^{126,140} Indoor O₃ concentrations are less correlated with outdoor concentrations, especially with the use of air conditioning.¹⁴¹ Given that the error in the exposure level should be independent of whether it was a case day or a control day, we would anticipate bias towards the null in our associations. A second limitation across all Aims is that exact time of stroke onset was unavailable. Misclassification of time of stroke onset has been shown to bias results toward the null when date of first presentation (at the hospital) is used instead.⁷¹

A limitation specific to Aims 1 and 2 was the lack of TIA data across time in the BASIC project. In the first iteration of BASIC, TIAs were collected during surveillance, but not in later iterations. Given that our results were not completely consistent with previous work in the study population in Aim 1, it would have been interesting to compare our results including TIAs across

the entire study period. However, TIAs are a challenging outcome to study, as by their definition, they are transient and may go unnoticed by the individual. Therefore, only TIAs that present to the hospitals could be captured for study, which would introduce ascertainment bias and may still not resolve our disparate results. For Aim 2, the sample size of recurrent strokes was small which may have limited our ability to detect associations and to identify vulnerable subgroups.

Selection bias may have played a role in our ability to detect associations between air pollution and stroke. Air pollution exposures could have also triggered death which would reduce the observed associations between air pollution and stroke if the survivors were less susceptible to the effects air pollution than those that had died. In the case of Aim 1, the associations that we observed between air pollution and incident ischemic stroke were conditional upon not having died from some other condition and not having a previous stroke; which perhaps, is more reasonable than the conditions required for inclusion in the Aim 2 study population. Recurrent strokes are a challenging group to study in general, but may be particularly challenging in short-term air pollution studies due to the links with other competing risks. Our definition of recurrent stroke was strict as one must have survived their previous stroke and that their next stroke was ischemic and observed within our study period. This may have resulted in underestimation of the air pollution stroke recurrence association if those most susceptible to air pollution did not survive to have a second stroke. Those that survive to have a second stroke may represent those that have some sort of resilience to the effects of air pollution.

Aim 3 had additional limitations. Our conclusions for the association of neighborhood disadvantage were based on it working separately from individual-level SES. While we included individual factors as confounders, we did not have data on individual-level SES. Previous studies have shown that neighborhood- and individual-level SES effects can be independent of one

another,^{164–166} but individual-level SES may still explain some of the differences we observed. Additionally, using census tract as a proxy for neighborhood may result in incorrect estimates of neighborhood disadvantage if the neighborhood characteristics are poor proxies of the construct of interest.¹⁶⁸ If census tracts do not reflect meaningful neighborhood areas, features relevant to severity, or represent the level of disadvantage, the ability to draw clear inferences on the effect of neighborhood disadvantage may be further limited.

5.5 Future Work and Considerations

The results of this dissertation could be expanded upon by future work in several ways. These are briefly outlined below.

Methodological Considerations

Additional methodological work could advance this area of research, specifically in regard to classification of air pollution exposures. While there was one ground-based air pollution monitor for the pollutants of interest during the course of the study, there have been advances in the field that may provide alternative methods to quantifying air pollution levels across space and time that could be incorporated into population-based studies such as BASIC. The REasons for Geographic And Racial Differences in Stroke (REGARDS) study utilized a mixture of ground-based pollution monitors and satellite measurements of aerosol optical depth (AOD) from the Moderate Resolution Imaging Spectroradiometer (MODIS) in estimating daily pollutant concentrations of PM_{2.5}.¹⁶⁹ Recent work has shown that AOD data has been successfully used to predict daily-surface-level PM_{2.5} concentrations^{169–171} and having a ground-based monitor to calibrate the algorithms improves the resultant modeled concentrations. Using the existing ground-based pollution monitors available in Nueces County, not only the one used in our analyses, but the other monitors that collected every third or sixth day concentrations, in

combination with satellite data, we could use existing algorithms to calibrate and estimate pollution concentrations with greater resolution for the stroke cases in BASIC. Satellite modeled daily levels of air pollutants have been shown to estimate acute health effects similarly to ground levels, and perhaps are more robust to estimating same-day and previous-day associations.¹⁷² These modeled concentrations at higher resolutions would allow spatial variation in exposure levels that had not been previously available. Having air pollution concentrations at greater resolution would allow for better characterization of overall air pollution-stroke associations as well as improving the estimation of ethnic-specific associations if there are spatial differences in where individuals of each ethnicity reside. The use of satellite data will not be as reliable as personal exposure measures, but will be a vast improvement on centrally located ground-monitor measured exposure.

Approaches used in this dissertation, specifically the case-crossover design and consideration of race/ethnic differences, could also be translated to other large, diverse population-based stroke studies such as the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) and the Northern Manhattan Study (NOMAS) to further our understanding of race/ethnic differences in susceptibility to air pollution. In Aim 1, we found some evidence of ethnic differences in the associations between PM_{2.5}, O₃, and incident stroke. As African Americans and other minority groups also face a greater prevalence of stroke risk factors, stress, and less access to healthy foods,^{8,168,173} increased susceptibility to the effects of air pollution might be expected. Specifically, using GCNKSS, one could evaluate whether black race modifies air pollution-stroke associations. NOMAS has a large population of predominantly Caribbean Hispanics and thus, one could investigate if Caribbean Hispanic ethnicity modifies air pollution-stroke associations. Replication of our findings in these other population-based studies

with well-defined stroke outcomes (as well as air pollution exposure) would be the next step in building evidence of race/ethnic differences in the association between air pollution and stroke. Should race-ethnic differences be identified studies could begin to examine mechanisms of enhanced susceptibility. If additional work in other race/ethnic groups supports our findings, this would argue that current standards are not protecting the population's most vulnerable subgroups and would argue for stricter standards.

Future Research on Environments and Stroke

We were the first study to demonstrate evidence of synergism between neighborhood disadvantage and air pollution on stroke severity and the next epidemiological step would be to replicate these results in another study population. Kleindorfer et al. found large differences in stroke severity across neighborhoods of varying levels of poverty in their study,¹⁷ but only used one year of severity data. It would be valuable to expand their data and to extend it to include air pollution concentrations and attempt to replicate our finding of a synergistic association between neighborhood disadvantage and air pollution concentrations on severity. However, the replication of synergistic associations of environmental factors does not have to be stroke specific. Prior studies in cardiovascular mortality have also observed a synergistic association between air pollution and neighborhood SES,^{97–100} and suggest that this association may exist for other cardiovascular endpoints. Replicating our findings of synergism between environmental factors would provide further support for environmental injustice; demonstrating that those in the most disadvantaged areas are at greater risk of negative health effects due to air pollution exposure provides a platform for regulatory and policy changes toward protecting individuals and areas equitably.

Additional exploration into ischemic stroke mechanism could explain some of the disparate findings of this dissertation and be an area of future study. Previous work has reported that air pollution levels are associated with large-artery atherosclerotic strokes, small-vessel occlusions, lacunar strokes, and TIAs rather than cardioembolic strokes.^{11,13,14,74} Differences in stroke mechanism could also explain why different ethnic groups may have differential susceptibility, and why some clinical risk factors may modify the air pollution-recurrence association. However, only one stroke etiology (cardioembolic strokes) has not been reported to have an association with air pollution and therefore it is unlikely that all differences are related to that subtype, and stroke mechanism can be difficult to obtain in large studies. The Trials of Org 10172 in Acute Stroke Treatment (TOAST) classification system is the most widely used for classifying stroke mechanism.¹⁷⁴ The classification of stroke subtype using the TOAST system is based on neurological signs, brain imaging findings, and other diagnostic tests. In surveillance studies, medical record information alone may be insufficient to accurately classify stroke mechanism. These challenges may make further investigation into stroke mechanism in large population-based studies difficult. However, some studies have stroke mechanism available. The NOMAS not only has stroke mechanism available, but also has a large population of Hispanics. NOMAS could be an ideal study population to investigate differences in the air pollution-ischemic stroke association by race/ethnicity and whether stroke mechanism explains differences in susceptibility.

The makeup of PM_{2.5} varies in constituents and toxicity. Some of the strongest associations between air pollutants and health outcomes have been observed with PM_{2.5} mass¹⁷⁵ but less is known in terms of what individual components are most associated with health-related toxicity.^{111,176,177} Recent work in Colorado reported that a collection of PM_{2.5} chemical

constituents were associated with cardiovascular disease related hospital admissions.¹⁷⁷ Ostro et al. identified several similar components of PM that were associated with cardiovascular mortality.¹¹¹ While daily availability of speciated PM_{2.5} is limited, as US EPA regulatory monitoring has focused on every third or sixth day, there has been increasing interest in promoting semi-continuous speciation collection for health studies.¹⁷⁸ Future work investigating the association between the chemical constituents of PM_{2.5} and stroke may be the missing link to understanding disparate associations between PM_{2.5} and stroke across studies.

Policy Implications and Interventions

The US EPA has just proposed to strengthen the NAAQS for ground-level O₃ based on current scientific evidence of the effects of O₃ on public health.¹⁷⁹ The Clean Air Act requires standards to be reviewed every five years to protect public health with an “adequate margin of safety”.¹⁷⁹ By changing the standard to a level lower than previous regulations, the EPA reported that the current standard of 75 ppb is not stringent enough to protect public health.¹⁷⁹ This dissertation is especially timely in conjunction with the EPA’s proposal, as we provide additional evidence that O₃ influences stroke risk, and may also influence stroke severity. Evidence of an O₃-stroke association is mounting,^{11,62,70,180} and suggests associations even at relatively low levels. While the EPA proposal suggests lowering the requisite standard to 65 to 70 ppb, these levels are still much higher than the observed levels in Nueces County (median 35.7 ppb). The proposal estimates that by strengthening the standard, there will be significant health benefits of \$7.5 to \$42 billion annually in 2025. These cost benefits go beyond reductions in stroke and stroke mortality, but also value avoidance of asthma, heart attacks, and premature death. Although the magnitude of the observed associations between O₃ concentrations and incident ischemic stroke and initial stroke severity may be modest, the number of strokes that are

attributable to O₃ may be high given that air pollution exposure affects almost everyone.

Assuming that the association between O₃ and incident ischemic stroke is causal and a linear function, a 20% reduction in the mean O₃ levels (7.4 ppb) during the study period may have averted approximately 6007 of the 387,000 stroke hospitalizations in the South region of US in 2010 alone.¹⁸¹

Evidence for differential effects of air pollution by ethnicity or other factors would have clear implications for social policy and for the US EPA mandate to set standards that protect sensitive populations. This dissertation focused in large part on indentifying sensitive populations. In Aim 1, we found a suggestive ethnic difference in the influence of PM_{2.5} and O₃ on stroke risk and in Aim 3, we identified that individuals living in more disadvantaged areas may suffer the effects of PM_{2.5} on stroke severity disproportionately. Our work could lead to additional research in diverse and disadvantaged areas, building evidence to support the need for environmental justice initiatives. These initiatives could be specific to Nueces County or to larger communities and geographies and could educate individuals on their rights to clean air and for being proponents toward fair enforcement of regulations. Community participation and buy-in is essential to develop, regulate and enforce initiatives that are sustainable to protect public health.

The identification of environmental and neighborhood level features that influence stroke and stroke severity lend themselves to potential public health interventions. Simple interventions, such as promoting awareness of high pollution days to at-risk individuals and educating the public on the health risks associated with high concentrations of pollutants and the effectiveness of high-efficiency particulate air (HEPA) filters,¹⁸² are possible avenues to target an entire community. In terms of severe strokes related to PM_{2.5} air pollution exposure, it would likely

take policy change or more equitable enforcement of air pollution regulations to reduce neighborhood disparities, as those in the most disadvantaged areas are likely suffering unjustly. Associations between O₃ and severity would also benefit from general reductions in exposure and uniform enforcement of regulations, as previously mentioned. The identification of high risk neighborhoods, those that are more disadvantaged, closer to major roadways, or closer to factories, would allow for such targeted interventions. Additional monitors would be necessary to identify these areas appropriately, but would also improve and inform future urban planning decisions. As regulatory decisions and interventions tend to move slowly, actionable interventions in high risk communities may promote health benefits faster.

This dissertation also suggests that enhanced monitoring of air pollution is needed not only in the most disadvantaged areas, but across all areas. Increasing the number of monitors in communities would allow for better characterization of the current exposure levels with greater resolution and in greater proximity to potential areas of high risk. Monitors are not always located in the most disadvantaged areas, which may actually have higher pollution levels than the a community as a whole.^{20,21} Monitoring EPA's attainment levels across both disadvantaged and non-disadvantaged areas would be a step towards promoting environmental justice. The increase in availability of data for pollutant levels in high risk areas would help to identify whether the most vulnerable are being protected adequately.

5.6 Conclusion

This dissertation identified that environmental features are important to understanding ischemic stroke risk and initial stroke severity. The results indicated that air pollution, an aspect of the physical environment, was associated with incident ischemic stroke and stroke severity, but not with recurrent stroke and that neighborhood disadvantage also influenced severity. The

influence of air pollution on stroke risk and severity may be differential by ethnicity and by neighborhood disadvantage level, respectively. Future studies and interventions are necessary to understand differential susceptibility to air pollutants and to promote environmental justice for areas that may not have the ability to protect themselves.

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